SURGERY
GYNECOLOGY AND OBSTETRICS

VOLUME 88 MARCH, 1949 NUMBER 3

CARCINOMA CELLS IN SPUTUM AND BRONCHIAL SECRETIONS

A Study of 150 Consecutive Cases in Which Results Were Positive

LEWIS B. WOOLNER, M.D., and JOHN R. McDONALD, M.D., Rochester, Minnesota

THE occurrence of grossly visible fragments of neoplastic tissue in the sputum of patients with cancer of the lung has been observed for many years. While such an occurrence is rare and usually indicates far advanced disease, an occasional diagnosis of bronchogenic carcinoma has been made by embedding and sectioning the tumor tissue so obtained. Betschart in 1895 reported a case of bronchogenic carcinoma in which the diagnosis was made by section of tumor fragments present in the sputum and cited 3 previous reports of cases in the literature. Similar diagnoses based on gross particles or "sputum section" were subsequently reported by a number of investigators including Sauerbruch in 1908, Bezançon and de Jong in 1913, Fishberg in 1926, Weller in 1929, Sweany in 1934, Hill in 1934, Edwards in 1934, and Holinger and associates in 1945. The technique employed by these workers involved ordinary histologic examination of tumor fragments or sputum, embedded and sectioned in the usual manner. In general the results were not considered of great value in the diagnosis of bronchogenic carcinoma.

The first report of the *cytologic* examination of sputum in a case of bronchogenic carcinoma was made by Hampeln (10) in 1887. He found large atypical epithelial cells in the sputum which he believed were diagnostic of carcinoma. His technique was simply the microscopic examination of unstained smears of fresh sputum. In a second paper in 1918 Hampeln (11) reported 25 cases of pulmonary cancer in 13 of which carcinoma cells were found in the sputum. Hampeln stressed the diagnostic importance of isolated neoplastic cells in contrast to other workers who held that a histologic section of an actual fragment of tissue was necessary for the diagnosis of carcinoma.

In spite of Hampeln's work, little attention was paid to the possibilities of cytologic study of sputum until the introduction of a new technique by Dudgeon and Wrigley of London in 1935. This method consisted essentially in

Abridgment of thesis submitted by Dr. Woolner to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Master of Science in Pathology.

From the Section on Surgical Pathology, Mayo Clinic.

Fig. 4 (frontispiece). a, Clump of cells in sputum from a bronchogenic carcinoma of undifferentiated type. Note the large size of the cells, variation in size, nuclear-cytoplasmic ratio and prominent nucleoli (hematoxylin and eosin stain ×800). b and c, Sputum smears from a keratinizing squamous cell bronchogenic carcinoma. Note voluminous eosinophilic cytoplasm in the cell in b, and the miniature whorl or cell nest in c (hematoxylin and eosin stain ×800). d and e, Carcinoma cells from a bronchogenic carcinoma of small cell "oat-cell" type. Note small size, absence of cytoplasm and variation in size of nuclei (hematoxylin and eosin stain ×800).

the making of films of fresh sputum, fixing, while wet, in Schaudinn's solution and staining with hematoxylin and eosin. The basis for this new technique was the "wet film" method of examination of fresh tissues described by Dudgeon and Patrick in 1927 and Dudgeon and Barrett in 1934. According to this procedure fresh tissues were scraped with a scalpel and the resulting suspension of cells transferred to a glass slide. Smears so obtained were fixed, while wet, in Schaudinn's fluid and stained with hematoxylin and eosin. By this means it was found possible to recognize malignant cells as such when separated from their usual surroundings. After eight years of experience with the wet-film method in the study of fresh tissues, Dudgeon and Wrigley employed the same technique to the study of sputum with equally successful results. In 68 per cent of 58 cases of proved carcinoma of the lung or respiratory tract, malignant cells were demonstrated in the sputum. In the majority of cases these authors were able to predict the histologic type of growth present in the bronchus by a study of the sputum. One false positive result occurred in this series, the atypical cells arising in an inflammatory lesion.

Using a similar technique Barrett reported positive results in 68 of 110 proved cases of bronchogenic carcinoma while Gowar obtained positive results in 64 per cent of 93 cases in which the sputum was investigated.

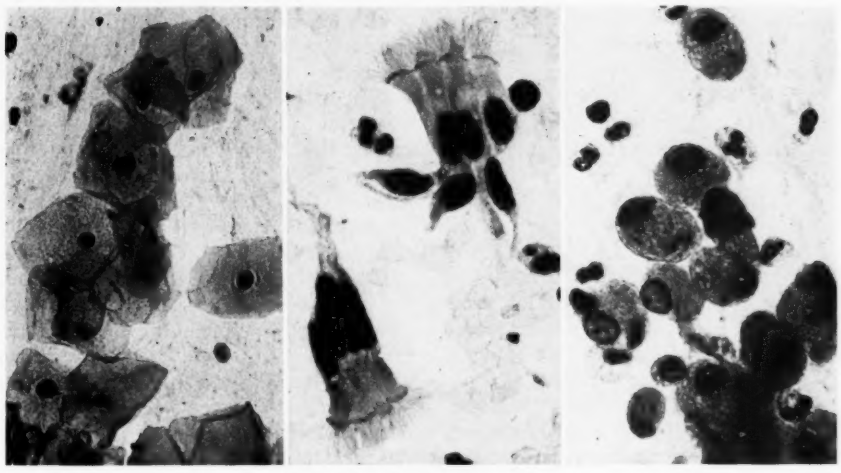
A very thorough study of the subject was reported by Wandall of Copenhagen in 1944. The material comprised 250 patients, 100 of whom had primary bronchogenic carcinoma. Of this group of 100 cases, carcinoma cells were found in the sputum in 84. The technique used was that of Dudgeon and Wrigley in which Schaudinn's fixative and hematoxylin and eosin stains were used. Eighty-two of the 100 patients with bronchogenic carcinoma underwent bronchoscopy. Biopsy gave positive results in 55 per cent. Examination of the sputum in this group gave the higher figure of 82 per cent positive results. Combining both these methods, Wandall found that a positive diagnosis of carcinoma could be made in 94 per cent of cases. Of 193 instances of sputum examination in which the clinical record was entirely unknown, a false positive result was given in 6, a percentile error of 3.1. Wandall concluded that a search for neoplastic cells in sputum should be introduced as an important link in the examination of patients believed to be suffering from primary bronchogenic carcinoma.

A study of bronchoscopically removed sections was carried out by Herbut and Clerf (12) in 1946. These authors expressed the belief that the examination of bronchial secretions is superior to the examination of sputum by reason of the increased dilution of the latter. Bronchoscopic removal of secretions from the region of the suspected tumor serves further to localize the source of the malignant cells. Positive results were obtained in 82.4 per cent of 57 proved cases of bronchogenic carcinoma. The results of bronchoscopic biopsy in this series were positive in 42 per cent. A positive diagnosis in 25 of their final 27 cases (92.5 per cent) led these authors (13) to conclude that in most cases of carcinoma of the lung the diagnosis can be made by means of cytologic study of bronchoscopically removed secretions.

Papanicolaou (16, 18, 19) for many years has stressed the value of the smear test as a basis for the diagnosis of malignant neoplasms having a free surface. While primarily concerned with cytologic study of vaginal secretions in the diagnosis of uterine cancer, he has reported results of sputum examination in 25 cases of carcinoma of the lung (17). In 22 of these cases (88 per cent), the sputum smears were positive for malignant cells. No false positive reports were given in this series.

PLAN OF THE PRESENT STUDY

The problems involved in this study were threefold: (1) to become familiar with the appearance of carcinoma cells in sputum and bronchial secretions as well as normal cells in all their variations, (2) to work out technical details of collection, smearing, fixation, and staining of material, and (3) to evaluate the method as a routine procedure to be used in the diagnosis of primary bronchogenic carcinoma. A preliminary period of study on sputum or secretions removed bronchoscopically from patients known to have carcinoma and from patients known not to have carcinoma



a b c

Fig. 1. Normal cells in sputum and bronchial secretions stained with hematoxylin and eosin. a, Squamous epithelial cells (×600). b, Ciliated columnar epithelial cells (×600). c, Pigmented macrophages (×640).

was carried out. In addition smears were made from bronchial secretions of lungs removed surgically for bronchogenic carcinoma. In other instances the surface of the tumor itself was gently scraped and the resulting emulsion of cells smeared, fixed, and examined. By this means familiarity with the appearance of carcinoma cells occurring apart from their normal environment was gradually acquired. Various methods of fixation and staining were tried to determine the best technique for routine laboratory work.

After this preliminary study, specimens of sputum or bronchial secretions were studied as unknowns and positive or negative results were reported. In doubtful cases, a second or even a third specimen was examined. In all, sputum or bronchial secretions were examined for carcinoma cells from a total of 1,600 patients. In 150 of these cases results were reported as positive and in 1,450 they were considered negative. No follow-up studies were done on the group of patients for whom the results were negative but the vast majority were considered to have nonneoplastic lesions. After positive results in 150 consecutive cases were reported the results were tabulated and analyzed.

TECHNIQUE

The methods of collection of specimens, preparations of smears, fixation, and staining have been outlined in a previous report by the authors (24). The staining method used routinely is Harris' hematoxylin with dilute eosin as a counterstain. It has proved entirely satisfactory for nuclear detail, the factor on which the diagnosis is primarily based, and has the advantage of familiarity to pathologists.

Examination of smears. Five smears from each specimen are fixed and stained according to the aforementioned technique. The films are then carefully scanned under low power, the high dry objective being used to study cell detail. It may be useful to mark suspicious cells or clumps with ink and later to return for careful consideration of these areas. The number of carcinoma cells per slide in a case of carcinoma varies considerably. In rare cases almost every low power field will show malignant cells. In many cases each slide will contain a few scattered clumps and isolated single cancer cells. Occasionally only one or two of the five slides will give positive results. For this reason it is important that all slides in a given case be examined methodically, a mechanical stage being used if necessary. The

time required for examination of films varies inversely with the number of atypical cells present. In some cases a positive diagnosis may be made almost at a glance or after 2 or 3 minutes' search; in others, in which few cells are present, 20 or 30 minutes may be required. Twenty to 30 minutes should be spent in a case in which the results are negative.

NORMAL CELLS IN SPUTUM AND BRONCHIAL SECRETIONS

Normal cells occurring in sputum and bronchial secretions fall into three main groups, namely, (1) epithelial cells, (2) macrophages, and (3) various inflammatory cells.

Epithelial cells. Epithelial cells in the sputum arise from the epithelial lining of the respiratory tract, mouth, and pharynx. Two types of epithelial cells are found, namely, squamous or pavement cells lining the mouth and pharynx and ciliated columnar cells from the trachea and bronchi. Squamous cells (Fig. 1a) are large polygonal cells with abundant faintly eosinophilic cytoplasm and a relatively small, round or oval nucleus. These cells are found in large numbers in sputum but rarely in bronchial secretions unless squamous metaplasia of the bronchial mucosa has occurred. They occur singly as a rule but occasionally in small groups. They present no diagnostic problem and are readily distinguished from squamous carcinoma cells.

Columnar epithelial cells (Fig. 1b) occur singly or in clumps and are readily recognized by their long slender shape, central oval nucleus and frequently well preserved cilia. Single cells of this type present no difficulty in diagnosis. Closely packed, solid collections of these cells, showing no trace of individual cell outline may be more difficult to identify with certainty. Such a clump may frequently be identified as bronchial epithelium by the presence of cilia, demonstrable at the periphery or on one border. The finding of a ciliated border automatically means that a given clump of cells is noncancerous. The uniformity in size and staining qualities of the nuclei in a clump of bronchial epithelial cells also points to their benign nature.

Macrophages. The phagocytic cells of the lung (Fig. 1c) occur with great regularity in sputum and bronchial secretions. These are the scavenger cells of the lung and are known by a variety of names, such as "dust-cells" or "heart-failure cells," depending on their content of phagocytized material. This may consist of various pigments, carbon, hemosiderin or granular debris. A vacuolated appearance of the cytoplasm results from the inclusion of fat droplets. The nucleus is small relative to the large amount of cytoplasm and is frequently eccentric in position. These cells are usually mononuclear although multinucleated forms are not uncommon. A distinct nuclear membrane is present, the chromatin network is delicate and one or two small nucleoli are usually seen. Macrophages tend to occur as isolated, mutually independent cells. Atypical clumps may sometimes cause confusion in diagnosis but can usually be identified as such by the occurrence of phagocytized material in the cytoplasm.

Inflammatory cells. These include a large variety of cells. Polymorphonuclear leucocytes are constantly present, occurring in large numbers in pulmonary suppurative disease. Eosinophils are seen mainly in bronchial asthma or other allergic states. Lymphocytes are frequently seen and must be differentiated from small cell "oat-cell" carcinoma. Plasma cells with typical nuclear chromatin pattern may be identified and occasionally large multinucleated cells resembling megakaryocytes are seen in sputum. Erythrocytes may occur in large numbers in both neoplastic and nonneoplastic disease of the lungs. The above mentioned varieties of cells should cause no confusion in interpretation, their appearance being essentially similar to that seen in ordinary blood films.

Familiarity with the normal noncancerous elements in sputum and bronchial secretions is a prerequisite to attempts at diagnosis of malignant cells. This is best accomplished by cytologic study of the sputum in a large variety of nonmalignant pulmonary diseases. In this study, specimens of sputum from a large number of patients who did not have carcinoma were examined. The patients from whom sputum was obtained included those who had pulmonary abscess, bronchiectasis, pulmonary tuberculosis, pneumonia and em-

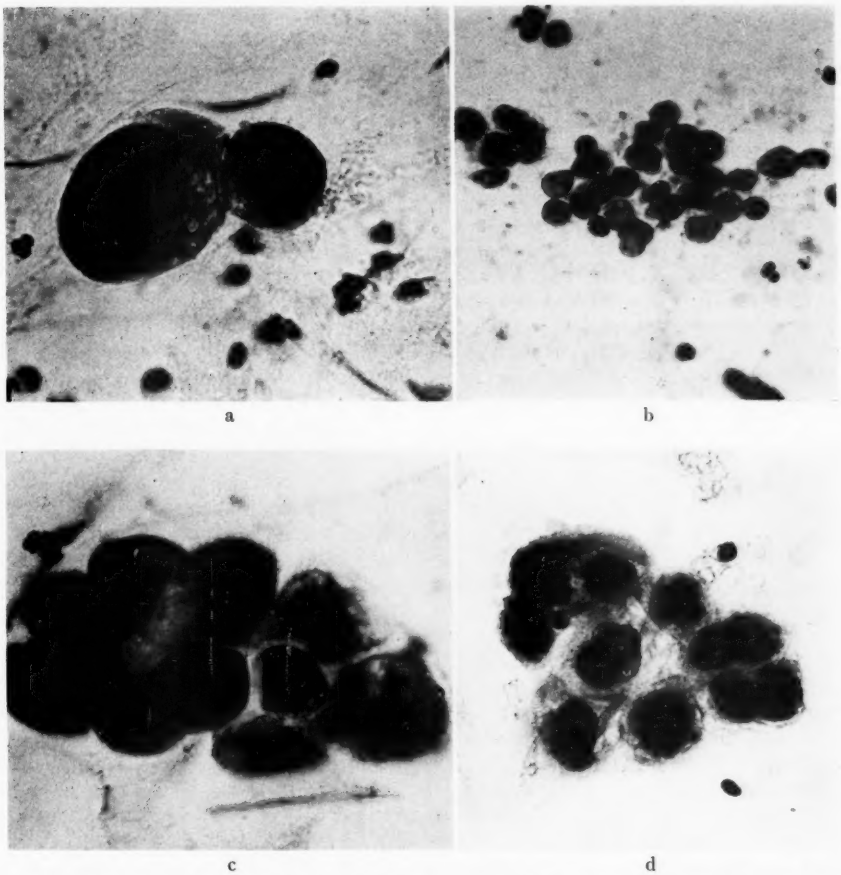


Fig. 2. Identification of exfoliated cancer cells in sputum or bronchial secretions (hematoxylin and eosin stain). a, Very large carcinoma cells in sputum. Compare size with that of adjacent polymorphonuclear leucocyte (×640). b, Sputum from bronchogenic carcinoma of small cell "oat-cell" type. Note small size of carcinoma cells and variation in size of nuclei (×640). c, Clump of carcinoma cells in sputum. Note variation in size of cells and mitotic figure (×640). d, Clump of carcinoma cells in bronchial secretions. Note very large nucleoli (×640).

pyema, bronchitis, bronchial asthma and congestive heart failure. Once familiarity is gained with the normal cells, carcinoma cells, because of their highly atypical appearance, can be diagnosed with confidence and with a high degree of accuracy.

CARCINOMA CELLS IN SPUTUM AND BRONCHIAL SECRETIONS

General characteristics of carcinoma cells. Exfoliated cancer cells in sputum or bronchial secretions possess certain distinctive features on which a diagnosis of malignancy can be safely based. In general it may be said that all the characteristic features of malignant cells seen in tissue sections, with the exception of invasion, can be applied to isolated cells, singly and in clumps, occurring in sputum and bronchial secretions. No single atypical feature is in itself diagnostic. The diagnosis is based on the complete cytologic picture in a given case, in which the cells may present

any or all of the following atypical characteristics.

Size.—Carcinoma cells are in general much larger than the normal cells in sputum or bronchial secretions. In some cases, cells of such enormous nuclear dimensions can be found (Fig. 2a) as to preclude any possibility of error in the diagnosis of malignancy. In other instances, the carcinoma cells while still large, more nearly approach the size of normal cells and more reliance must be placed on other atypical features. In the small cell "oat-cell" type of bronchogenic carcinoma the cells fall well within the range of size of normal cells, the nucleus being only two or three times the diameter of a lymphocyte (Fig. 2b).

Nuclear cytoplasmic ratio. More important than the size of the cell itself is the size of the nucleus and the relation of nucleus to cytoplasm. In the malignant cell the nucleus is very large in relation to the amount of cytoplasm. In some highly undifferentiated tumors the relatively large nucleus is surrounded by a narrow rim of cytoplasm; in others, as in the small cell carcinomas, the carcinoma cell frequently appears as a naked nucleus. An exception to this general finding is seen in the cells of a keratinizing squamous cell carcinoma. Many of these cells show voluminous acidophilic cytoplasm indicating keratinization of individual cells.

Variation in size and shape.—Variation in size and shape of the nuclei is an extremely important consideration. This can best be appreciated when small clumps or clusters of carcinoma cells are present (Fig. 2c). Small clumps of malignant cells are a frequent finding in smears and, although not essential for a diagnosis of malignancy, aid greatly in the ease of interpretation. Clumps of benign cells present a regularity of size, shape, and staining of the nuclei not seen in neoplastic tissue. Variation in size and shape of the cells is probably least marked in small cell carcinomas, but even in this type sufficient variation is present to differentiate these cells from normal. In sputum or secretions from highly malignant tumors, variation in cell size may be extreme and tumor giant cells may be seen.

Variation in staining.—Carcinoma cells possess distinctive staining properties which are as apparent in smears as in tissue sections. Nuclei of carcinoma cells generally are hyperchromatic and show a coarse chromatin network. In many cases carcinoma cells possess unusually large, often multiple nucleoli of irregular shape and size (Fig. 2d). The nucleoli may appear basophilic or acidophilic and, when prominent, offer a definite aid in diagnosis. Details of nuclear structure are most important and for this reason a uniform and consistent staining technique must be developed. It should be noted that good nuclear detail may not be present in all atypical cells found in the smear. Careful search may be necessary to find well preserved cells with characteristic features on which a diagnosis of carcinoma may be safely based.

Mitotic figures.—In general, cells undergoing mitosis are rarely found in smears of sputum or bronchial secretions and are of no importance in the diagnosis of carcinoma by this technique. Even in rapidly growing tumors, as shown by tissue section, mitotic figures are rarely found in the exfoliated cancer cells examined in the smear.

Special characteristics of carcinoma cells according to histologic type. Exfoliated cancer cells vary somewhat in appearance according to the histologic type of tumor present in the bronchus (Figs. 3, 4, frontispiece, and 5). These tumors can be classified into four main groups: (1) small cell "oat-cell" carcinoma, (2) undifferentiated large cell carcinoma, (3) squamous cell carcinoma in which cell keratinization or pearly body formation is noted, and (4) adenocarcinoma characterized by the production of mucus or by gland formation. To these should be added so called alveolar cell carcinomas representing a small group of primary pulmonary neoplasms and presenting a characteristic gross and histologic pattern.

Carcinoma cells are found in the sputum in all these types and in certain instances are sufficiently distinctive to predict the histologic type of tumor in the bronchus. This is true especially of small cell carcinomas and keratinizing squamous cell carcinomas. In other cases, especially in highly undifferentiated tumors, a diagnosis of "carcinoma cells present" is made without reference to type. Occasionally the problem arises as to whether a given

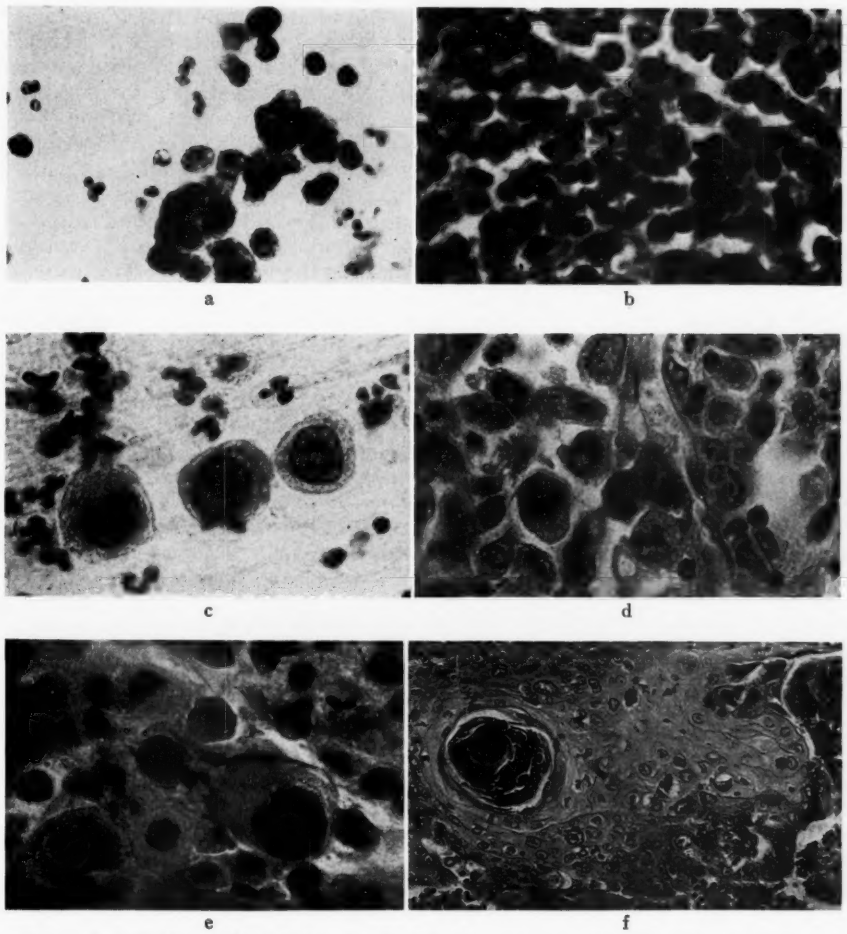


Fig. 3. Readily identified histologic types of exfoliated carcinoma cells in sputum (hematoxylin and eosin stain). a, Sputum smear from a bronchogenic carcinoma of small cell "oat-cell" type (×640) and, b, corresponding tissue section (×640). Note similarity of cells. c, Carcinoma cells in sputum from an undifferentiated large cell bronchogenic carcinoma showing large nuclei and prominent nucleoli (×640) and, d, corresponding tissue section (×640). e, Smear from bronchogenic carcinoma of squamous type showing large amount of cytoplasm and, f, tissue section of keratinizing squamous cell carcinoma (×165).

pulmonary tumor is primary or metastatic. The presence of small "oat-cell" or squamous carcinoma cells may in such cases aid in establishing a diagnosis of primary bronchogenic carcinoma. If the malignant cells in the sputum possess no distinctive features the primary or secondary nature of the tumor must be assessed in the light of the whole clinical picture.

Small cell bronchogenic carcinoma.—Exfoliated carcinoma cells from a small cell bronchogenic carcinoma are readily detected by the smear technique. The cells are small in size as compared with carcinoma cells of other types but nevertheless stand out prominently under the low power objective, frequently in clusters or streaks across the slide. Occurring in this fashion, they are readily detected under

low magnification whereas a single cell might escape notice. Under the high power objective the main features of note are the small size of the cells, the virtual absence of cytoplasm and the hyperchromatism of the nuclei (Fig. 3a). Definite variation in size of the nuclei from cell to cell is a very important criterion in diagnosis. The nuclear chromatin forms a coarse network. Nucleoli are usually not prominent in carcinoma cells of this type. The appearance of the cells in tissue sections of this type of bronchogenic carcinoma is shown in Figure 3b.

Undifferentiated bronchogenic carcinoma.—Carcinoma cells in sputum from an undifferentiated bronchogenic carcinoma with corresponding tissue section are shown in Figure 3c and d. In such cases the carcinoma cells are large with marked variation in size and shape of the nuclei. The nucleus is large in relation to the cytoplasm, is hyperchromatic, and contains prominent nucleoli. Cells of this type occurring singly as shown here provide adequate evidence for a diagnosis of carcinoma. Clumps of carcinoma cells, although not essential, aid greatly in the ease of diagnosis. A clump of cells from an undifferentiated bronchogenic carcinoma is shown in Figure 4a. These cells exhibit all the characteristics of malignancy seen in a tissue section (except invasion) including large size, marked variation in size and shape of nuclei, hyperchromatism and very large nucleoli.

Squamous cell carcinoma.—Exfoliated cancer cells from a squamous cell bronchogenic carcinoma are shown in Figure 3e and a corresponding tissue section is shown in Figure 3f. In this type the carcinoma cells are large with irregularity in size and shape of the nuclei. The cytoplasm is frequently abundant and is deeply eosinophilic depending on the degree of keratinization of the cells (Fig. 4b). Inclusion of one cell in another suggestive of a beginning whorl or cell nest is a rather frequent finding (Fig. 4c). As is true of small cell carcinoma, the cytologic characteristics of sputum from a patient with a keratinizing squamous cell carcinoma is usually distinctive enough to predict accurately the histologic type of tumor to be found in the bronchus.

Adenocarcinoma.—In Figure 5a is shown a clump of neoplastic cells in a bronchial aspiration which exhibit a tendency toward an acinar arrangement. The tissue section in this case revealed an adenocarcinoma of the bronchus (Fig. 5b). The occurrence of such a large fragment of tissue showing a glandular arrangement is distinctly unusual in sputum or bronchial secretions. Occasionally, however, an abnormal vacuolation of the cytoplasm indicating the production of mucus points to a diagnosis of adenocarcinoma. In most cases of adenocarcinoma a diagnosis of "carcinoma cells present" is made without any indication of type.

Alveolar cell carcinoma.—In 2 cases in this series, atypical cells were found in the sputum and the roentgenologic appearances were those of alveolar cell carcinoma involving both lungs. No tissue was obtained in either of these cases. In a third case, one lobe only was involved. The sputum contained carcinoma cells (Fig. 5c). Bronchoscopic examination gave negative results. The excised lobe was diffusely involved with alveolar cell carcinoma (Fig. 5d).

Metastatic tumor of the lung.—In a few cases in this series, carcinoma cells in the sputum were probably of metastatic origin. In 1 instance bronchial secretions contained large plaques of tumor cells of undifferentiated type. A tumor of the testis had been removed 2 years previously and the growth in the lungs was presumably metastatic. In 1 case the bowel and in another the ovary were considered the primary sources of the tumors. Differentiation of primary from secondary tumor of the lung is usually impossible on the basis of smears although the presence of "oat cells" or squamous carcinoma cells in the sputum represents fairly good evidence of a primary bronchogenic carcinoma.

ANALYSIS OF CASES

This study is based on 150 cases in which carcinoma cells were found in sputum or bronchial secretions. It does not represent the findings in a consecutive series of 150 bronchogenic carcinomas. An exact statistical study was not attempted since secretion or sputum was not available in all cases and in

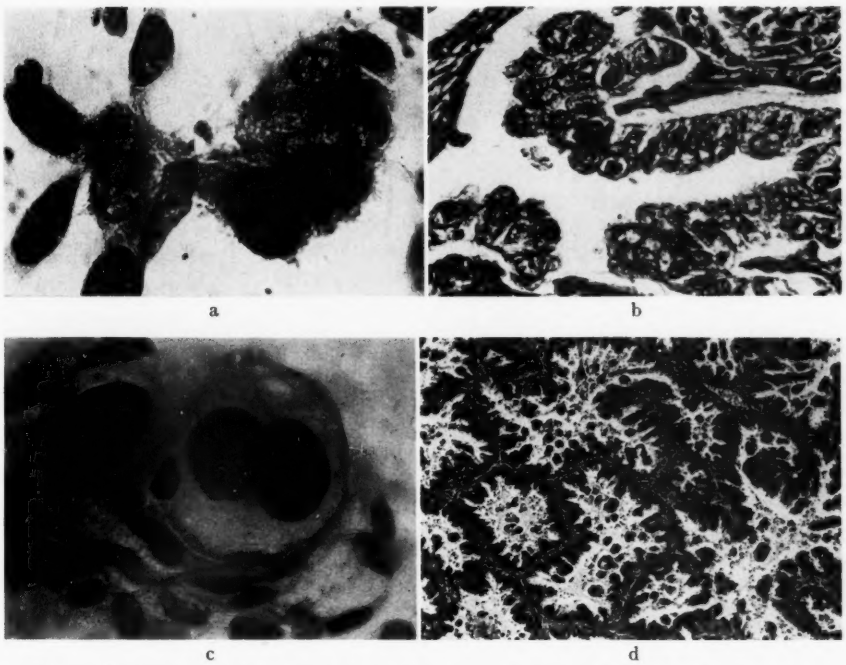


Fig. 5. Adenocarcinoma of the bronchus and alveolar cell carcinoma of the lung (hematoxylin and eosin stain). a, Carcinoma cells in bronchial secretions from a bronchogenic carcinoma of the adenocarcinoma type showing suggestion of gland formation (×640) and, b, tissue section from same lesion (×325). c, Carcinoma cells in bronchial secretions (×640) and, d, tissue section from an alveolar cell carcinoma of the lung (×65).

some instances the material submitted for examination was inadequate. The method of study adopted was to collect 150 cases in which sputum or bronchial secretion was positive for carcinoma cells, and by an analysis of these cases to evaluate the accuracy of the method and its usefulness as a routine diagnostic procedure.

Source of carcinoma cells in sputum. The majority of cases in this series represented proved or suspected bronchogenic carcinoma. In 146 of 150 cases the source of the malignant cells was believed to be a tumor of the bronchus. Carcinoma cells, however, may appear in the sputum from a malignant lesion anywhere in the respiratory tract, pharynx, or esophagus. In 2 cases in this series the sputum contained malignant cells arising from an esophageal carcinoma. In both, a tracheoesophageal fistula was demonstrated and the nature of the lesion proved by biopsy. In 1 case the trachea and in another the larynx were found to be the source of the carcinoma cells found in the sputum. The latter patient gave a history of several months hoarseness with recent slight hemoptysis. Biopsy revealed a squamous cell carcinoma of the larynx. One disadvantage of sputum examination is this failure to localize the lesion. In contrast to examination of sputum, examination of bronchial secretions has the advantage that the source of the malignant cells, particularly the side involved, can be more accurately determined.

Comparison of sputum and bronchial secretions. A comparison of sputum and bronchial secretions as a source of carcinoma cells reveals no essential advantage of one over the other. In a given case of bronchogenic carcinoma, the specimen of sputum submitted may

occasionally be negative for carcinoma cells while the bronchoscopically removed secretions prove positive. This was found to be true in 10 cases of a total of 110 cases of bronchogenic carcinoma in which the sputum was examined. The reverse (sputum positive and bronchial secretions negative for carcinoma cells) was found to be true in 6 of 80 cases in which bronchial secretions were examined. A negative result on sputum examination in a case believed clinically to be carcinoma should be followed by a second, and, if necessary, a third sputum examination. This assures an adequate sampling of the sputum and greatly reduces the possibility of a false negative report. If bronchial secretions submitted in a suspected case of bronchogenic carcinoma are negative for carcinoma cells, subsequent examination of the sputum should be carried out. If the results of sputum examination prove positive while the results of examination of bronchial secretions are negative, it is assumed that the secretions were not aspirated from the bronchus involved by the carcinoma. Both methods of examination should be utilized whenever possible.

Accuracy of diagnosis. In this series of 146 cases of suspected pulmonary neoplasm, a final diagnosis of primary bronchogenic carcinoma was established by bronchoscopic biopsy in 64 cases and by surgical exploration in 24 cases. In 2 additional cases in which the results of bronchoscopic biopsy were positive, the pulmonary lesion was considered metastatic. Autopsy, biopsy of supraclavicular nodes, punch biopsy, and section of expectorated tissue provided proof of the diagnosis in 7 cases. In 3 cases a false positive report was given on the basis of the findings in the smears; the absence of carcinoma was proved in 2 of these cases at operation and in 1 at necropsy. In the remaining 46 cases carcinoma was not proved by tissue section since tissue was not available. In all 46 cases, carcinoma cells were found in the sputum or bronchial secretions. All patients presented symptoms related to the chest and evidence of carcinoma on roentgenologic examination of the lungs.

In 22 of these 46 cases additional evidence of bronchogenic carcinoma was presented in the finding of clinical or roentgenologic evidence of metastasis. In 8 additional cases a tumor was visualized by the bronchoscopist although positive results at biopsy were not obtained. In 11 cases a diagnosis of inoperable bronchogenic carcinoma was made on the basis of history, clinical findings, and roentgenologic evidence in the chest, supported by demonstration of carcinoma cells in the sputum. In 1 case, the final diagnosis was primary bronchogenic carcinoma or ovarian carcinoma with metastasis to the lungs. In 2 cases the disease was diagnosed alveolar cell carcinoma or metastatic malignant lesions to both lungs. In 1 case of long standing pulmonary suppurative disease, roentgenologic findings in the chest were those of extensive cavitation of the upper third of both pulmonary fields. Sputum studies for acid-fast bacilli gave negative results but cytologic studies showed numerous carcinoma cells present. Bronchoscopy failed to locate any malignant process. No follow-up on this patient was available. In 1 case the final diagnosis was empyema or bronchogenic carcinoma and no further information could be secured. In all cases except the last 2, the diagnosis of a malignant process in the lung was considered to be beyond doubt. All lesions were considered inoperable or operation was recommended and refused. In the last 2 cases the clinical impression favored a nonmalignant process but atypical cells were found in the sputum smears.

In review, of 150 cases in which the smears were reported positive for carcinoma cells, in 145 there was a final diagnosis of carcinoma, in 3 cases the final diagnosis was disease other than carcinoma (proved false positive reports) and the final diagnosis in 2 cases was not established.

Value of the method as an adjunct to established methods of diagnosis. This study indicates that the cytologic study of sputum and bronchial secretion is a valuable adjunct in the diagnosis of bronchogenic carcinoma. Of the 146 patients with suspected bronchogenic carcinoma, 114 were examined bronchoscopically. In this group a specimen for biopsy was obtained in 97 cases and the results of biopsy were positive for carcinoma in 66 cases. Thus, of the group of 114 cases in which bron-

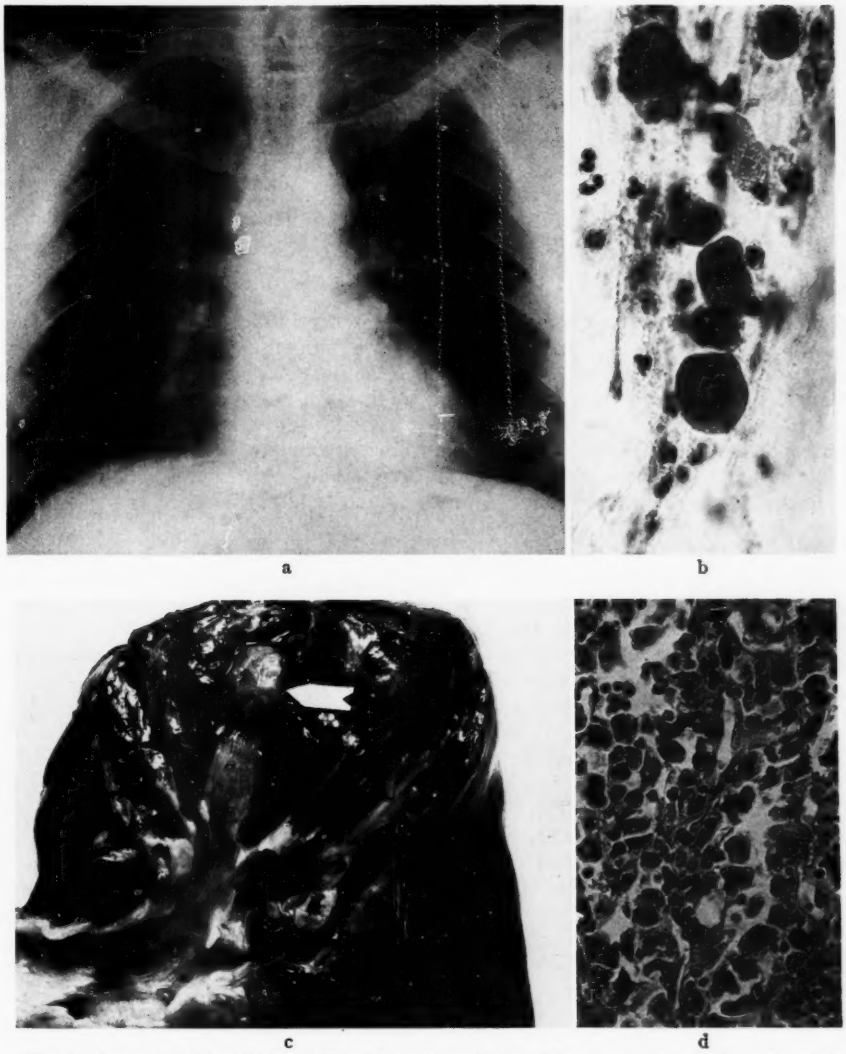


Fig. 6. Case 1. Peripherally located bronchogenic carcinoma. Lung removed surgically on basis of, a, roentgenologic shadow and, b, carcinoma cells in sputum (hematoxylin and eosin stain ×640). c, Lesion indicated by arrow. d, Tissue section (hematoxylin and eosin stain ×300).

choscopy was performed, cytologic studies on sputum or bronchial secretions provided the only microscopic basis for a diagnosis of carcinoma in 48 cases (42 per cent).

Surgical exploration was carried out in 58 cases in this series. In 31 of these, the results of preoperative bronchoscopic biopsy were positive while in 25 cases bronchoscopic biopsy could not be performed or the results were negative. Positive results on examination of smears of sputum or bronchial secretions, however, provided a preoperative diagnosis of carcinoma. In this group, two of the three false positive diagnoses were made. In

1 case bronchoscopic examination revealed a tumor projecting from the upper lobe bronchus. Bronchial secretions contained atypical cells interpreted as carcinomatous. Lobectomy revealed stenosis of the upper lobe bronchus with multiple lesions of caseous tuberculosis throughout the lobe. In the second case, bronchoscopic examination showed obstruction of the right middle lobe bronchus. Lobectomy was carried out and diffuse bronchiectasis was found in the middle and lower lobes. In the remaining 56 cases in this group bronchogenic carcinoma was demonstrated at operation. In 24 of these cases the lesion proved to be removable. Pneumonectomy or lobectomy for bronchogenic carcinoma was performed on the basis of positive results of bronchoscopic biopsy in 15 of the 24 cases. In 9 cases bronchoscopic biopsy gave negative results or could not be performed and a preoperative diagnosis of carcinoma was based on the cytologic characteristics of the sputum or bronchial secretions. Of the 9 bronchogenic carcinomas excised on a basis of positive cytologic findings, 5 were situated in the upper lobes, 1 in the right middle lobe, 2 in the lower lobes and 1 proved to be an alveolar cell carcinoma diffusely involving the whole left lower lobe of the lung.

Lesions of the upper lobe. Because of the inaccessibility of many upper lobe lesions for bronchoscopic biopsy, study of smears of sputum or bronchial secretions provides an especially useful adjunct to diagnosis in this group. In 19 cases of this series the site of the lesion could not be accurately located. In 41 or almost a third of the remaining cases the lesion was situated in the upper lobes. Diagnosis of bronchogenic carcinoma was established by bronchoscopic biopsy in 12 of these 41 cases. Cytologic diagnosis of carcinoma on the basis of sputum or bronchial secretions was confirmed by surgical exploration in 14 cases and by autopsy, punch biopsy, or lymph node biopsy in 3 additional cases. In 12 cases the dismissal diagnosis was bronchogenic carcinoma, inoperable. In 3 of these 12 cases roentgenologic or clinical evidence of metastasis was present.

Inoperable lesions in the diagnosis of which a bronchoscopic examination is not indicated. In 32 cases of suspected bronchogenic carcinoma, a bronchoscopic examination was not carried out. In these cases roentgenologic or clinical evidence of metastasis, pleural effusion, or other signs of inoperability were presented. In such cases sputum examination provides a convenient method of confirming the clinical diagnosis of bronchogenic carcinoma. A sputum examination, the results of which are negative or inconclusive in the face of good clinical evidence of carcinoma, should be repeated several times if necessary. In 1 case in this series, carcinoma cells were found in the fourth specimen of sputum examined. The diagnostic importance to be attached to negative results on examination of sputum or bronchial secretion depends on the situation of the lesion. In general, a hilar lesion associated with repeatedly negative results on sputum examination is almost certainly not carcinoma. A very peripherally located bronchogenic carcinoma may or may not be associated with malignant cells in the sputum, depending on the accessibility of the desquamated cells to the bronchial tree.

False positive results of examination of sputum or bronchial secretions. In this series a false positive report on the basis of smears was given in 3 cases. In 2 additional cases the final diagnosis was not established. In 2 of the 3 cases in which proved false positive results were obtained, lobectomy was performed. In 1 case bronchial stenosis and caseous tuberculosis were found. In the second, bronchiectasis of the middle and lower lobes was present. In the third case roentgenograms of the lungs revealed a diffuse process in the bases of both lungs which was believed to be inflammatory. Cytologic examination of the sputum disclosed atypical cells interpreted as carcinoma cells. At autopsy, extensive pulmonary infarction was found in addition to an organized pneumonic process in both lungs. The mucosa of the large bronchi was the site of squamous metaplasia and marked epithelial proliferation, with numerous mitotic figures in the hyperplastic epithelial cells.

Erroneous diagnoses may occur with this technique in the early period of investigation before sufficient experience with the method

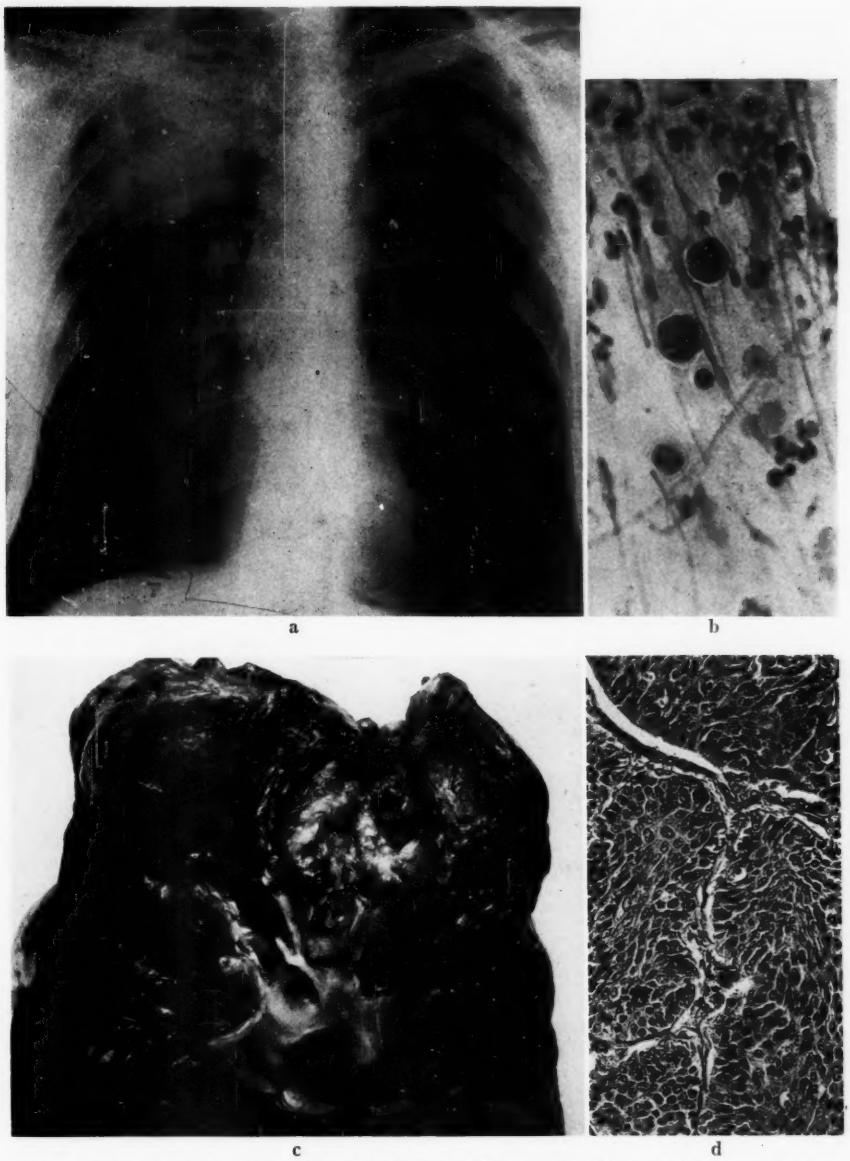


Fig. 7. Case 2. Bronchogenic carcinoma of the upper lobe. Lesion in the upper lobe inaccessible for the purpose of bronchoscopic biopsy. a, Roentgenologic appearance. b, Carcinoma cells in sputum (hematoxylin and eosin stain ×640). c, Gross lesion. d, Tissue section (hematoxylin and eosin stain ×130).

has been acquired. Errors at this stage are the result of inexperience of the examiner rather than a result of deficiencies of the method. After familiarity with the method has been gained, diagnosis by means of smears becomes accurate and reliable.

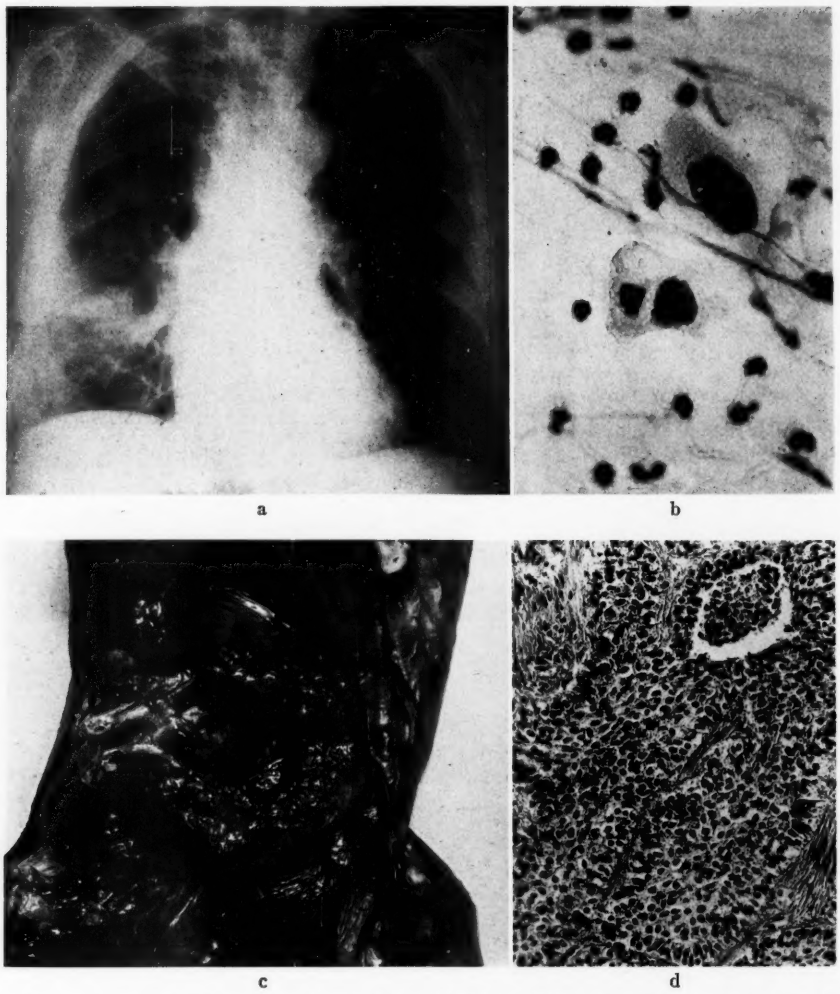


Fig. 8. Case 3. Bronchogenic carcinoma of the middle lobe. Diagnosis based on carcinoma cells in sputum. a, Roentgenologic appearance. b, Carcinoma cells in sputum (hematoxylin and eosin stain ×640). c, Gross lesion. d, Tissue section (hematoxylin and eosin stain ×130).

REPORT OF ILLUSTRATIVE CASES

CASE 1. *Peripheral bronchogenic carcinoma.* A 39 year old white man complained of fever, malaise, night sweats, and weight loss of 1 month's duration. Symptoms relating to his chest were minimal, consisting of slight hemoptysis and pain in the left axilla for 2 days before admission. Results of roentgenologic examination of the chest (Fig. 6a) were reported as follows: "Pathologic process left apex, probably tuberculosis but rule out primary malignancy." Bronchoscopic examination gave negative results. The sputum was negative for acid-fast bacilli and fungi. Clinically the picture did not suggest malignancy but had many features of an acute infectious process. The skin test and serum agglutination test were positive but blood cultures were negative for Brucella. The problem was solved by a cytologic examination of sputum which showed carcinoma cells (Fig. 6b). The lung was resected and a small lesion was found in the apex (Fig. 6c) measuring less than 2 centimeters in diameter. In spite

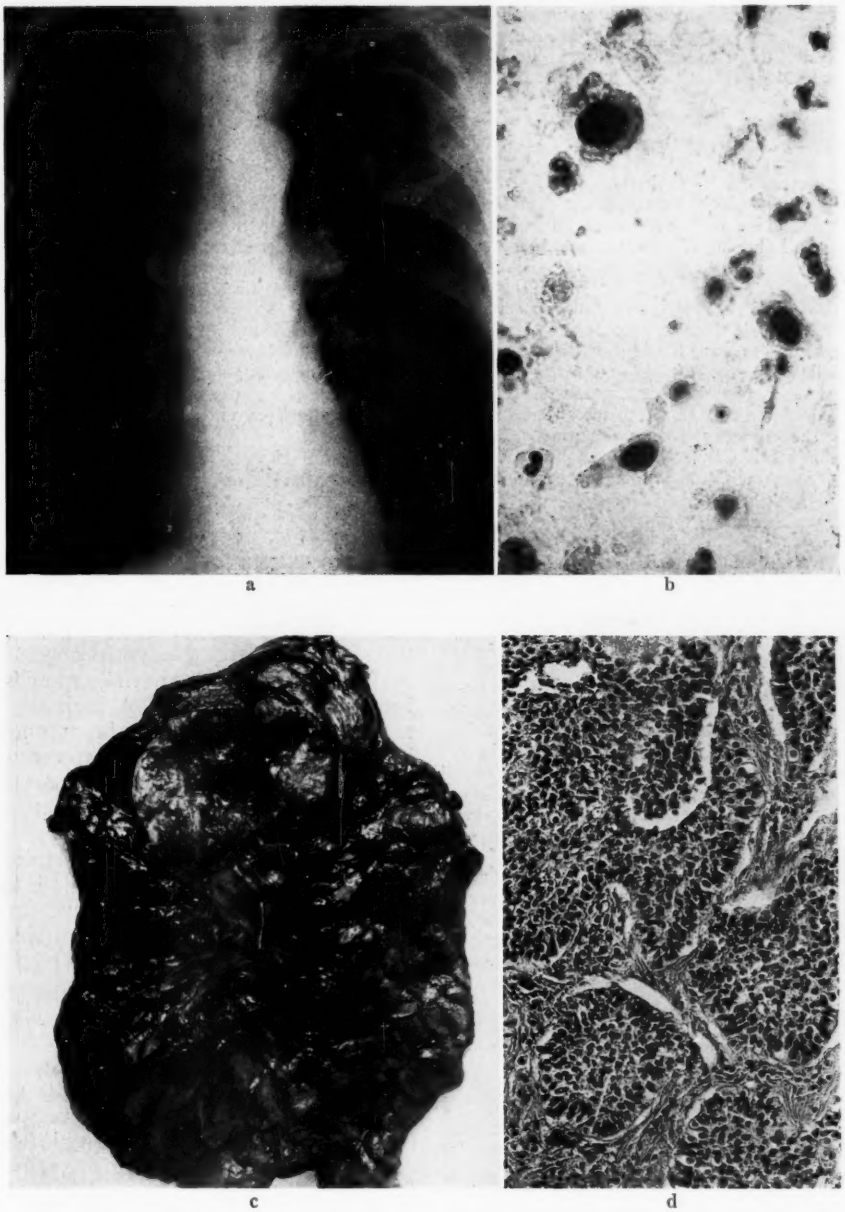


Fig. 9. Case 4. Carcinoma in a bronchogenic cyst. Finding of carcinoma cells in sputum provided a preoperative diagnosis of carcinoma. a, Roentgenologic appearance. b, Carcinoma cells in sputum (hematoxylin and eosin stain ×650). c, Gross lesion. d, Tissue section (hematoxylin and eosin stain ×130).

of its very peripheral location, large numbers of carcinoma cells were being discharged in the sputum. Histologically the tumor was a highly undifferentiated bronchogenic carcinoma (Fig. 6d).

CASE 2. *Bronchogenic carcinoma of the upper lobe.* A 56 year old man registered at the clinic because of pain in the right side of the chest and cough of about 4 months' duration. Roentgenograms of the chest revealed a mass in the posterior segment of the right upper lobe, bronchogenic carcinoma to be ruled out (Fig. 7a). Bronchoscopy was carried out with the following report: "I was unable to get out far enough in the right upper lobe bronchus to visualize a growth. The right upper lobe bronchus seemed to be fixed." Specimen for biopsy could not be obtained. Sputum was negative for acid-fast bacilli and fungi but was found to contain many carcinoma cells (Fig. 7b). A right pneumonectomy was performed and pathologic examination disclosed a bronchogenic carcinoma 5 centimeters in diameter involving the bronchus of the right upper lobe (Fig. 7c). Tissue section revealed a squamous cell carcinoma (Fig. 7d). No involvement of the lymph nodes was found.

CASE 3. *Peripheral bronchogenic carcinoma of the right middle lobe.* A 71 year old woman complained of a chronic dry cough of 8 months' duration. The patient had had a cough each winter for several years which cleared up each time after the cold weather. Nine months before admission she had had an episode of pain in the lower part of the right side of the chest which extended up under the right scapula. No hemoptysis was noted at any time. The patient felt well and had gained weight. Roentgenograms of the chest (Fig. 8a) revealed "thickened pleura with residual fibrosis in the right base." Sputum studies were negative for acid-fast bacilli but cytologic studies were positive for carcinoma cells (Fig. 8b). A bronchoscopic examination was carried out with the following report: "I was unable to visualize any tumor in the right lower lobe." Surgical exploration was done on the basis of the sputum findings and a tumor of the right lung was palpated. Because of the patient's age, the surgeon elected to do a middle and lower lobe lobectomy. Pathologic examination revealed a small bronchogenic carcinoma involving one of the bronchi of the right middle lobe (Fig. 8c). Histologic section showed a squamous cell carcinoma (Fig. 8d). The patient had an excellent postoperative course and was dismissed in good condition.

CASE 4. *Carcinoma in a bronchogenic cyst.* A 54 year old white man was admitted to the clinic because of cough, pain in the chest, and hemoptysis of 2 months' duration. For the past 6 to 8 months he had noted listlessness, loss of 10 pounds (4.5 kgm.), occasional fever and night sweats. His past history revealed several attacks of pneumonia and pleurisy. Sputum examination for acid-fast bacilli and tuberculin skin tests gave negative results. Results of roentgenologic examination of the chest (Fig. 9a) were reported as follows: "There is a large, rather well circumscribed cavity in the left upper lobe without a great deal of surrounding reaction. Some fibrosis in left apex. Rule out bronchogenic carcinoma with cavitation." The story of respiratory difficulty of long duration and the roentgenologic appearance of the lesion strongly suggested a bronchogenic cyst. However, an examination of the sputum revealed carcinoma cells in great numbers (Fig. 9b). A bronchoscopic examination was not carried out. The preoperative diagnosis was carcinoma of the left upper lobe with cavitation. A left pneumonectomy was performed and the pathologic examination of tissue removed revealed a squamous cell carcinoma 4 by 3 by 2 centimeters in the wall of a bronchogenic cyst 6 centimeters in diameter (Fig. 9c). Histologic section (Fig. 9d) showed a squamous cell carcinoma. No lymph nodes were found involved. One small bronchus opened into the cyst, providing a pathway for the carcinoma cells to reach the sputum. The postoperative course was uneventful.

COMMENT

This study would indicate that cytologic examination of sputum and bronchial secretions is an extremely valuable adjunct in the diagnosis of carcinoma of the lung. Carcinoma cells may be distinguished from normal cells in the smear by a variety of atypical features including large size, variation in size and shape particularly of the nuclei, hyperchromatism, and large nucleoli. A high degree of accuracy of diagnosis may be accomplished by this method as is shown by the occurrence of only 3 proved false positive reports in 150 cases in which a diagnosis of carcinoma was made by the smear technique.

The interpretation of smears requires considerable experience but, once this is gained, the test has great practical value. In practice a microscopic diagnosis of carcinoma is frequently established within an hour of receiving the specimen at the laboratory. It provides microscopic evidence of malignancy in many cases in which proof is otherwise not obtainable.

Many bronchogenic carcinomas, particularly lesions of the upper lobe and peripherally located neoplasms, are not accessible for bronchoscopic biopsy. In this series 114 patients underwent bronchoscopic examination. In 17 of these material for biopsy could not be obtained. In 31 cases the tissue removed for biopsy proved to be nonneoplastic while in the remaining 66 cases a microscopic diagno-

sis of bronchogenic carcinoma was made on the tissue removed. Obviously any method which would serve to supplement bronchoscopic examination and provide microscopic proof of the presence of carcinoma when biopsy cannot be performed would be of immense practical importance in the diagnosis of pulmonary neoplasms. It has been shown that cytologic study of sputum and bronchoscopically removed secretions provides this microscopic proof in the majority of these inaccessible lesions. By combining both methods in the examination of the patient with suspected bronchial carcinoma a much higher rate of positive diagnoses can be accomplished than heretofore has been the case.

The ability to make a microscopically proved diagnosis of cancer in a higher percentage of cases will serve to reduce materially the preoperative diagnosis of "indeterminate pulmonary lesion." In this series exploration for bronchogenic carcinoma was carried out in a total of 58 cases. Of this number, in 31, or 53.4 per cent, carcinoma was diagnosed on the basis of bronchoscopic biopsy. In 25 cases, cancer cells in the sputum or secretions provided the only microscopic evidence of malignancy. In 2 cases a false positive diagnosis was given on the basis of smears.

Furthermore, by use of the smear technique, a positive microscopic diagnosis of carcinoma may be made in many cases of suspected bronchogenic carcinoma in which a bronchoscopic examination is not indicated. In 32 cases no bronchoscopic examination was carried out. The demonstration of carcinoma cells in the sputum in these cases was a valuable confirmation of the clinical and roentgenologic evidence of primary bronchogenic carcinoma.

The need for earlier diagnosis of cancer of the lung is shown by the low rate of resectability of these lesions. In this series 24 bronchogenic carcinomas were removed in a total of 143 cases of suspected malignant disease. More widespread use of cytologic examination of sputum for cancer cells offers a hope of earlier detection of bronchogenic carcinoma before the lesion has progressed to an inoperable stage. Because of the vital importance of earlier diagnosis, it is felt that every patient with an undiagnosed lesion of the chest should be given the benefit of a carefully conducted cytologic examination of sputum or bronchial secretions for cancer cells.

SUMMARY

The purpose of this study was the identification of cancer cells in sputum or bronchial secretions and evaluation of the smear technique as a routine procedure in the diagnosis of bronchogenic carcinoma.

The technique employed was based on the original work of Dudgeon and Wrigley. Sputum was examined while fresh or it was collected in a few cubic centimeters of 95 per cent alcohol. Five smears were made from each specimen. The smears were fixed, while wet, in equal parts of absolute alcohol and ether for 30 minutes. The staining method adopted was Harris' hematoxylin followed by dilute eosin as a counterstain.

Smears of sputum or bronchial secretions from nonneoplastic diseases of the lung revealed squamous and ciliated columnar epithelial cells, macrophages, and various inflammatory cells.

Carcinoma cells in smears could be distinguished from normal cells by numerous atypical characteristics including large size, variation in size and shape of the cells and of the nucleus, the nuclear-cytoplasmic ratio, hyperchromatism of the nucleus, and the presence of large nucleoli.

The appearance of carcinoma cells in sputum and bronchial secretions varies with the histologic type of tumor in the bronchus. Cancer cells originating in a bronchogenic carcinoma of small cell "oat-cell" type or in a keratinizing squamous cell type provide the most distinctive morphologic characteristics. A diagnosis of the histologic type of tumor present was usually possible in the case of these two cell types. In most other bronchogenic carcinomas, especially the more undifferentiated tumors, a diagnosis of "carcinoma cells present" was made without reference to histologic type.

Metastatic lesions of the lungs may be the source of carcinoma cells in sputum or bronchial secretions.

Analysis of 150 cases in which the smears were diagnosed positive for carcinoma cells

was carried out. In 146 of these cases the source of the atypical cells was believed to be a tumor in the bronchial tree. In 141 of the 146 cases a final diagnosis of primary or metastatic carcinoma of the lung was made. In 3 cases diagnoses made on the basis of smears were proved to be false positives. In 2 cases the final diagnosis, whether inflammatory or neoplastic, was not definitely established.

Carcinoma cells in sputum or bronchial secretions provided the only preoperative microscopic evidence of cancer in 25 (43 per cent) of a total of 58 cases in this series in which surgical exploration was carried out.

Of 24 cases of bronchogenic carcinoma in which the lesion could be removed, cancer cells in the smears provided the only microscopic evidence of cancer in 9 cases (37 per cent).

REFERENCES

1. Barrett, N. R. J. Thorac. Surg., 1938, 8: 169–183.
2. Betschart, Erasmus. Virchows Arch., 1895, 142: 86–100.
3. Bezançon, Fernand, and de Jong, Samuel Israëls. Traité de l'examen des crachats. Pp. 282–284. Paris: Masson et Cie, 1912.
4. Dudgeon, L. S., and Barrett, N. R. Brit. J. Surg., 1934, 22: 4–22.
5. Dudgeon, L. S., and Patrick, C. V. Brit. J. Surg., 1927, 15: 250–261.
6. Dudgeon, L. S., and Wrigley, C. H. J. Lar. Otol., Lond., 1935, 50: 752–763.
7. Edwards, A. T. J. Thorac. Surg., 1934, 4: 107–124.
8. Fishberg, Maurice. Arch. Int. M., 1926, 37: 745–772.
9. Gowar, F. J. S. Brit. J. Surg., 1943, 30: 193–200.
10. Hampeln, P. St. Petersburg. med. Wschr., 1887, n. F., 4: 137–139.
11. Idem. Mitt. Grenzgeb. Med. Chir., 1918–1919, 31: 672–718.
12. Herbut, P. A., and Clerf, L. H. J. Am. M. Ass., 1946, 130: 1006–1012.
13. Idem. Med. Clin. N. America, 1946, 30: 1384–1392.
14. Hill, R. M. Edinburgh M. J., 1934, 41: 320–333.
15. Holinger, P. H., Hara, H. J., and Hirsch, E. F. Ann. Otol. Rhinol., 1945, 54: 1–36.
16. Papanicolaou, G. N. Science, 1942, n. s. 95: 438.
17. Idem. J. Am. M. Ass., 1946, 131: 372–378.
18. Papanicolaou, G. N., and Marshall, V. F. Science, 1945, n. s. 101: 519–520.
19. Papanicolaou, G. N., and Traut, H. F. Diagnosis of Uterine Cancer by the Vaginal Smear. New York: The Commonwealth Fund, 1943.
20. Sauerbruch, E. F. J. Am. M. Ass., 1908, 51: 808.
21. Sweany, H. C. Ann. Otol. Rhinol., 1934, 43: 561–571.
22. Wandall, H. H. Acta chir., scand., 1944, 19 (suppl. 93): 1–143.
23. Weller, C. V. Arch. Path., 1929, 7: 478–519.
24. Woolner, L. B., and McDonald, J. R. Proc. Mayo Clin., 1947, 22: 369–381.

CLINICAL RESPONSE OF METASTATIC LESIONS OF CARCINOMA OF THE FEMALE BREAST TO HORMONAL THERAPY AS RELATED TO HISTOLOGIC GRADE OF MALIGNANCY

ELIZABETH LOWENHAUPT, M.D., and HOWARD L. STEINBACH, M.D.,
San Francisco, California

HORMONAL therapy is a recognized method of control of remote lesions in carcinoma of the female breast (2). The clinical response is not uniform and various factors have been cited as influencing the prognosticated response. Thus Nathanson states, in regard to stilbesterol, that favorable responses are confined to older women and that in younger women the disease is unaltered or perhaps accelerated. Halberstaedter and Hochman report that typical adenocarcinomas are more susceptible to treatment with estrogens than are anaplastic tumors. Their conclusion, however, is based on pathologic reports with no uniform terminology and no attempt at detailed grading. For these reasons it seems of interest to correlate histologic evidence of growth rate (and by inference physiologic maturity) with the observed response to physiologic modes of treatment.

MATERIAL AND METHODS

Clinical material and therapeutic methods are described in a report by one of the authors (HLS, 8). All cases of this report in which histologic material was available are included here. These cases, 27 in all, 17 treated with estrogens and 10 with testosterone, are summarized in Tables I and II.

Without being aware of the clinical data, one of us (EL) reviewed all of the sections and graded[1] the tumor according to the criteria shown by Greenough to be of prognostic worth. This author has shown the following five points to be evidence of low malignancy: (1) marked adenomatous pattern, (2) marked secretion by cells, (3) uniformity of cell appearance and size, (4) uniformity of nuclear size, and (5) lack of nuclear hyperchromatism and of mitotic figures. Accordingly the maximum of each category was given the grading four plus and the minimum zero, the five averaged and the tumor assigned to an arbitrary group: low malignancy, three plus or over; medium, two plus; and high, one plus or less —using the nearest whole figure. This material is summarized with the clinical data in Tables I and II. Examples of each of these groups are shown in Figures 1 to 6.

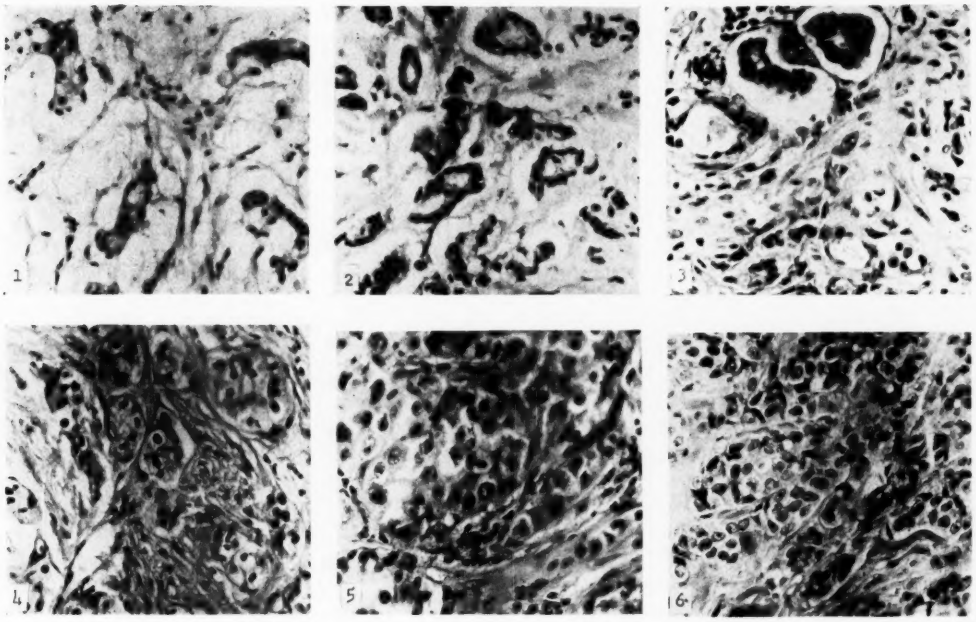
RESULTS

The large percentage of tumors of high malignancy in this series does not represent carcinomas of the breast in general; those of lower grades are probably cured by radical surgery. Thus, this represents a distortion. However, in this series, although most carcinomas in younger age groups are highly malignant, the reverse is not true, contrary to accepted belief (3). As shown in Figure 7, there were 5 highly anaplastic tumors after 60 years. This is of importance in determining the type of treatment, the decision at present being made primarily on clinical data. This will be discussed below.

In summarizing it was found that because of its use in the young age group, in most of the patients receiving testosterone the tumors were of high malignancy (8). Of these only one responded, the growth remaining temporarily stationary. The tumors in 2 patients showing clinical improvement (O.S. and

From the Divisions of Pathology and Radiology, University of California Hospital.

[1]Histologic grading, to be sure, is at best an approximation and a sort of average of many fields and sections. However, it soon becomes evident that each tumor, although not uniform, tends to fit into one class. The two extremes are well separated, though there is, of course, some overlap in the central group. This is brought out in Figures 1 through 6. In a very few instances the tumor in the lymph node differed in degree of malignancy from the primary, in which instances the grading of the metastasis was considered as representing the lesion under treatment.



Figs. 1 to 6. Histologic grading of carcinoma of the female breast. (Hematoxylin and eosin, ×200.) The figures are arranged in order of increasing malignancy. Information concerning these examples is shown in the following table. (It is to be noted that details of grading of this particular area might differ from that shown in Tables I and II, though the class and total remain the same.)

Fig.	Case	Glands	Secretion	Uniformity of		Lack of mitoses	Class	Response
				Cell	Nucleus			
1	B. S.	++	++++	+++	+++	+++	Low	Improved with testosterone
2	I. W.	++++	+	+++	+++	+++	Low	Improved with estrogen (axillary mass regress)
3	M. R.	++	o	+++	+++	+++	Medium	Skin nodes disap. with estrogen. No recurrence
4	F. T.	+	+++	++	+	++	Medium	Pulm. met. regress, no change in axillary mass
5	M. W.	+	++	+	+	o	High	Lesions progress with estrogens
6	F. W.	o	+	+	+	o	High	Lesions progress with estrogens

B.S.) were of medium and low malignancy. The improvement in these patients refers to osseous metastases (8), and this will be discussed further below.

A similar trend was found in respect to the patients treated with estrogens. Thus the 2 patients with tumors of low malignancy improved, 5 of the 8 of medium and only 1 of the 7 of high grading. The results for the whole series are shown graphically in Figure 8.

DISCUSSION

Testosterone, the substance of choice in young women (1, 7, 8) and of use in control of osseous metastases (1), acts by way of its effect on calcium metabolism (1), "snowing under" still living tumor cells. It is to be expected, and is borne out by this series, that more slowly proliferating tissue would be more effectively buried in new forming bone. Those tumors of high malignancy, predicted as non-

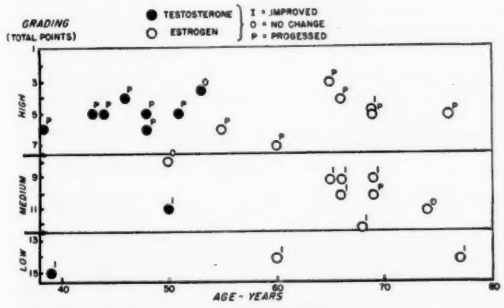


Fig. 7. Malignancy as related to age and to clinical response. Tumors in young women are in general of high malignancy and there is a gradual fall with advancing age. However, 5 tumors of high malignancy occurred here in women over 60 years. Also shown is the fact that only 1 tumor of high malignancy improved with hormonal therapy, while only 1 of medium or low malignancy progressed.

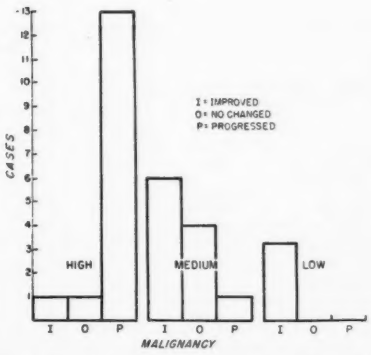


Fig. 8. Response of all hormone treated carcinomatous metastases as related to degree of malignancy.

responsive, might well receive concomitant roentgen therapy to local bone lesions (8).

Estrogens, of use in older women (7, 8), are effective in control of metastatic soft tissue lesions of low and low medium malignancy (Figs. 1 to 6). The decision as to treatment, then, cannot be made on the basis of age alone, for highly malignant tumors are present in old women (Fig. 7, F.W., aged 76). These soft tissue lesions will not be controlled by estrogens and might well receive concomitant x-ray therapy from the outset or as symptoms occur (8). It is a matter of conjecture as to the effect of testosterone on bone lesions in elderly people with osteoporotic skeletal systems in which anaplastic cells are proliferating.

Of interest is the history of a long period of cure, with late recurrence of remote lesions of medium malignancy (16 years in the case of M.Ro., 17 years in the case of M.Ra). It seems likely that the original metastatic cells

TABLE I.—RESULTS AFTER TESTOSTERONE TREATMENT

Case Age	Known time since original carcinoma	Metastases	Histology of tumor					Grade	Response	Conclusion
			Glands	Secretion	Uniformity of Cell	Uniformity of Nucleus	Lack of mitoses			
B.S. 39	26 months	Skin, lung, ribs	++	++++	+++	+++	+++	Low	Subcutaneous—no change. Decrease cough and chest pain	Improved
M.K. 53	3½ years	Bone	o	o	+	++	+	High	Relief of pain. No change by x-ray	No change
V.S. 38	3½ years	Lung, liver	o	+++	+	+	+	High	Died 4 months	Died
A.C. 51	1½ years	Skin, lung	o	++	+	+	+	High	Symptoms worse	Died
M.T. 44	3 years	Lung, bone	o	o	+	++	++	High	Lesions progressed	Died
D.J. 46	2 years (R) 3 weeks (L)	Liver, spine	+	o	+	+	+	High	Pain less. Died 2 weeks	Died
O.S. 50	7 years	Bone	+++	o	+++	++	+++	Med.	Complete relief of pain, bone healing by x-ray	Improved
A.J. 48	8 years (L) 5 months (R)	Skin	+	++	+	+	+	High	Progressed in skin, lymph node and liver metastases appear	Died
E.S. 43	4½ months	Lymph node	o	o	+	++	++	High	Increased size of nodes	Progressed
E.P. 48	5 years	Skin	++	o	+	+	+	High	New lesions appear	Progressed

+=1 plus

TABLE II.—RESULTS AFTER ESTROGEN TREATMENT

Case Age	Known time since original carcinoma	Metastases	Histology of tumor					Grade	Response	Conclusion
			Glands	Secretion	Uniformity of		Lack of mitoses			
					Cell	Nucleus				
B.T. 77	5 years (R) 3 years (L)	Lung	+++	++	+++	+++	+++	Low	X-ray signs in lung disappear	Improved
B.B. 74	9 years	Bone	++	+++	++	++	++	Med.	Pain less, but no x-ray changes	No change
M.Ro.68	7 years	Axillary	+++	++	++	++	+++	Med.	Decrease size of mass	Improved
J.N. 50			+	++	++	+	++	Med.	Questionable relief	No change
M.Ra. 66	16 years	Three skin nodules	+	o	+++	+++	+++	Med.	Nodules disappear	Improved
E.K. 69	4 years	Bone	+++	+	++	++	++	Med.		Progressed
A.B. 55	7 months	Bone	+	o	++	++	+	High	Increased pain	Died
F.W. 76	3 years	Lung, hilar nodes	+	+	+	+	+	High	Increased x-ray size	Progressed
M.W.66	4 years	Axillary nodes, lungs	o	++	+	+	o	High	Increased size	Progressed
J.H. 69	1 year	Skin, lymph nodes	o	+	+	+	++	High		Died
I.W. 60	10 years	Skin, opposite breast, axillary nodes	++++	+	+++	+++	+++	Low		Improved
F.T. 65	3 years	Lung, bone	+	+++	++	+	++	Med.	Lung regress (bone progress)	Improved
E.F. 60	3 years	Axillary, lung	+	+	++	++	+	High	Axillary nodes, no change. Lung lesions regress, but return after 2 months	Progressed
J.G. 66	4 years	Skin, lymph nodes, lung, liver, bone	++	+	+++	++	+	Med.	Skin disappear. L. nodes smaller	Improved
E.D. 69	2 years	Skin, lymph nodes	+	++	++	++	++	Med.	Decreased skin nodules	Improved
I.T. 65	2 years	Skin, lymph nodes, lung, bone	o	o	+	+	+	High	All lesions increasing	Progressed
C.T. 69	2 years	Skin, axillary nodes	++	+	+	+	o	High	Skin lesions disappear. Axillary nodes smaller	Improved

+=1 plus

may well have been of slow growth rate, or quiescent, with only recent, more rapid growth and perhaps change of histologic pattern, perhaps in a changing environment.

SUMMARY

Response of remote metastases of carcinoma of the female breast to hormonal therapy is correlated with the histologic grade of malignancy, tumors of low grade responding most favorably. Degree of malignancy cannot be predicted on the basis of age. It is suggested that information obtained by biopsy examination be used as an additional factor in determining the clinical management of each patient.

REFERENCES

1. ADAIR, F. E. Surg. Gyn. Obst., 1947, 84: 719-722.
2. Council on Pharmacy and Chemistry. J. Am. M. Ass., 1947, 135: 987-989.
3. EWING, J. E. Neoplastic Diseases. 4th ed., p. 565. Philadelphia: W. B. Saunders Co., 1940.
4. GREENOUGH, R. B. J. Cancer Res., 1925, 9: 453-469.
5. HALBERSTAEDTER, L., and HOCHMAN, A. J. Am. M. Ass., 1946, 131: 810-816.
6. HADDOW, A., WATKINSON, J. M., and PATERSON, E. Brit. M. J., 1944, 2: 393-398.
7. NATHANSON, I. T. J. Cancer Res., 1946, 6: 484.
8. STEINBACH, H. L. et al. (In press.)

THE "VERTICAL EPIDEMIC" OF MAMMARY CARCINOMA IN MICE

Its Possible Implications for the Problem of Cancer in General

LUDWIK GROSS, M.D., New York, New York

OBSERVATIONS have been made recently on mouse mammary carcinoma which may fundamentally influence our approach to the problem of cancer in general. These observations can be summarized as follows:

There exist families of mice in which, in each successive generation, practically all middle aged females develop mammary carcinomas (48, 26, 50, 51, 52, 9, 11, 4, 5). These animals are for all practical purposes in perfect health during their early adult age, although they are earmarked to die from cancer. They develop tumors upon reaching approximately one to one and a half years of age. The causative agent responsible for the development of breast cancer is transmitted in these tumor-families of mice from one generation to another through the milk of nursing mothers (10, 14, 17, 1).

A SIMPLE METHOD OF PREVENTING BREAST CANCER IN MICE

The development of mammary carcinomas in otherwise susceptible mice of the tumor-families can be prevented by the simple measure of isolating the newly born animals from their tumor-agent carrying mothers, and transferring them for the purpose of nursing to females whose milk is free from the invisible mammary carcinoma agent. Such foster-nursed animals grow up and remain healthy despite the fact that they are direct descendants of a tumor-family. They live their normal life spans and do not develop breast tumors. Moreover, their milk is also free from the tumor agent; they can, in due time, nurse their own litters naturally, without transmitting to them the seed of the fatal disease (10, 14, 17, 1).

On the other hand, female mice that belong to families free from mammary carcinoma, can be infected with the invisible tumor agent by ingesting, in early infancy, milk containing the mammary carcinoma factor. The infection can be accomplished experimentally by placing such newly born mice under the care of a foster mother whose milk contains the tumor factor. Such infected animals grow up, and remain apparently healthy; they harbor, however, the tumor agent, and transmit it to their progeny. When these animals reach the tumor age, they develop and eventually die from mammary carcinomas. In the meantime, however, their progeny has grown up, and has, in turn, transmitted the tumor agent to the next succeeding generation.

BIOLOGICAL PROPERTIES OF THE TUMOR AGENT

The mammary carcinoma agent present in the milk of females of certain high tumor lines of mice, earmarked to develop breast tumors later in life, is so small as to be invisible under an ordinary, optical microscope. The agent is filterable through a bacteria-tight Seitz filter (19, 7).

The agent is present not only in the milk of female mice earmarked to develop mammary carcinomas, but also in the tumor cells (15). When such tumors are transplanted, by graft, from one animal to another, they carry with them the tumor agent which can later be extracted from such tumors after several successive transplantations (21). The agent is present in the mammary tissue (13, 6) of mice earmarked to develop mammary carcinomas, less constantly in certain organs of such animals (12, 6), and occasionally also in their blood (59). The simplest method of obtaining the agent is to grind a mammary tumor, whether

From the Cancer Research Unit, Veterans Administration Hospital, Bronx, New York.

Published with the permission of the Chief Medical Director, Department of Medicine and Surgery, Veterans Administration, who assumes no responsibility for the opinions expressed or conclusions drawn by the author.

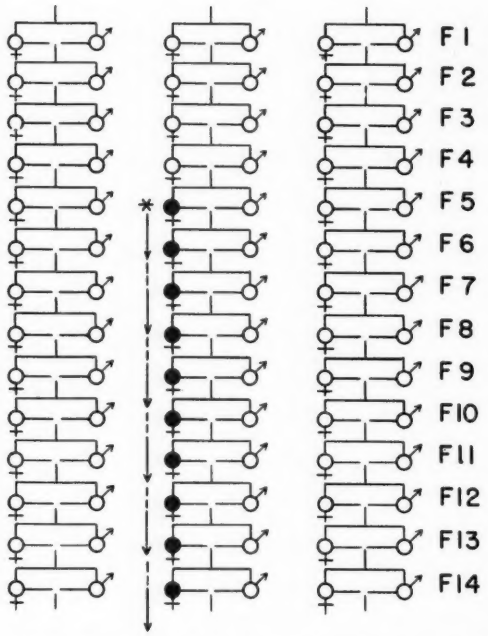


Fig. 1. The spread of mammary carcinoma following exposure, that is, the ingestion of milk containing the tumor agent.

spontaneous or transplanted, with physiological sodium chloride solution, and then separate the agent from the tumor cells by centrifugation at low speed. The agent is present in the supernatant fluid. A few drops of such a fluid fed to newly born mice, by an eye dropper, or a simple feeding device (40), will result in the development of "spontaneous" mammary carcinomas in these animals a year and a half later. In the meantime, however, these animals will have already transmitted the agent, through milk, i.e. "naturally" to their own progeny.

Oral administration of the agent is effective, and results in the eventual development of tumors, provided the animals ingest the virus in early infancy, i.e. when 1 to 28 days of age. Feeding of adult or middle aged animals with either milk or extracts from tissues containing the tumor agent, results occasionally only, if at all, in the development of mammary carcinomas (6, 20). Subcutaneous or intraperitoneal (7) injection of the agent into young animals is an excellent means of producing experimentally spontaneous mammary carcinomas; when older animals, however, are injected, they will develop tumor much less frequently, or not at all (3, 6, 20, 23), unless massive doses of the virus are inoculated (23).

The tumor agent is destroyed by heating to 61 degrees C. for 30 minutes. Thus, the agent would not resist pasteurization (7, 8).

The tumor agent has antigenic properties (7, 31). Following injection of the agent (i.e. a mouse mammary carcinoma extract) into a rabbit, no tumors, of course develop in these animals; the serum of such a rabbit, however, acquires the property of neutralizing the agent in vitro. When such an immune serum is incubated, in a test tube, at room temperature, for 2 hours with mouse mammary carcinoma agent, it neutralizes it; the mixture injected into mice will not produce tumors. The neutralization is specific; normal rabbit serum, for instance, will not neutralize the tumor agent (7, 31); neither will the mammary carcinoma agent be neutralized by a serum obtained from a rabbit that had been injected with a different tumor (7), or with normal mouse organs (31).

The various biological properties of the mouse mammary carcinoma agent discussed above appear to suggest that this agent is a virus.

MAMMARY CARCINOMA OF MICE— A COMMUNICABLE DISEASE

Thus, in mice at least, mammary carcinoma can be acquired in early infancy by ingestion of an extraneous, transmissible, agent. Once acquired, the disease is self-propagating from one host to another through the milk of nursing females. The chain of transmission of mammary carcinoma in a family of mice can be interrupted, however, by isolating the newly born animals from their potentially cancerous mothers and preventing them from ingesting the tumor agent. In other words, mouse mammary carcinoma can be acquired by exposure (Fig. 1). Once acquired, it becomes self-perpetuating from one host to another; the acquisition of the disease can be prevented, however, by isolation (Fig. 2).

Upon reviewing these facts dispassionately, it is difficult to avoid the conclusion that breast cancer of mice is a communicable disease (33).

THE VERTICAL PATTERN OF TRANSMISSION OF MOUSE MAMMARY CARCINOMA AGENT

When comparing the pattern of transmission of mammary carcinoma of mice with that of many common communicable diseases, several differences become apparent. In the case of measles, smallpox, or typhoid fever, the transmission of the infectious agent occurs among hosts that, in most instances at least, belong to the same generation; thus, an infected host placed in close quarters with other, healthy, but susceptible individuals of practically any age, will often transmit the infecting agent to its companions. In the case of mouse mammary carcinoma, however, the causative agent is, as a rule, transmitted among hosts belonging to successive generations. A mouse carrying the tumor agent, and bearing a large, exposed, perhaps already ulcerated mammary carcinoma, can be placed in the same cage with healthy, susceptible mice, yet, no transmission of the disease will result. The same tumor-bearing mouse, however, will transmit the tumor agent, through milk, to her own daughters, and through these to her granddaughters, great-granddaughters, and so forth, i.e. to hosts of successive generations. The term "vertical epidemic" has been suggested for this type of transmission of extraneous, parasitic agents (33).

In mouse mammary carcinoma the exposure and infection occur early in infancy. This is followed by apparent health, lasting at least through the early adult life of the host; during that time the disease spreads to the next group of hosts, which belongs to the next succeeding generation. The symptoms of the disease (tumors) appear in most instances at the end of the life cycle of the host, i.e. after the transmission of the causative agent has been assured; this is followed by death of the host. Thus we have (1) exposure and infection, followed by (2) a very long asymptomatic phase of apparent health coupled with (3) the ability of the host to transmit the disease to other individuals, and, finally, (4) appearance of symptoms of disease, and (5) death of the host.

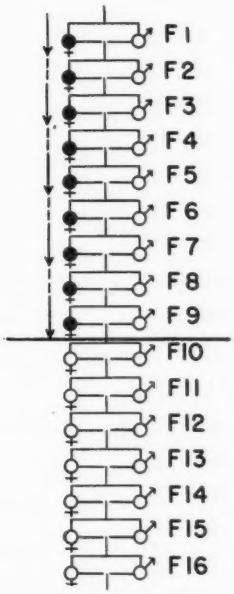


Fig. 2. Arresting the vertical transmission of mammary carcinoma in mice by isolation, that is foster nursing, preventing the ingestion of milk containing the tumor agent.

This pattern is essentially different from that observed in the majority of common communicable diseases, where, following (1) exposure and infection (which may occur at almost any time during the life cycle of the host), very promptly (2) symptoms of the disease appear, coupled with (3) the simultaneous ability of the host to transmit the infectious agent to other susceptible individuals belonging, as a rule, to the same generation; (4) either death, or recovery of the host follows.

THE "SKIPPING" OF GENERATIONS IN THE TRANSMISSION OF MOUSE MAMMARY CARCINOMA

Despite these differences, there are certain common traits between these two patterns. Both groups of diseases are caused by extraneous, parasitic agents. In both instances, an individual may harbor the agent, and actually

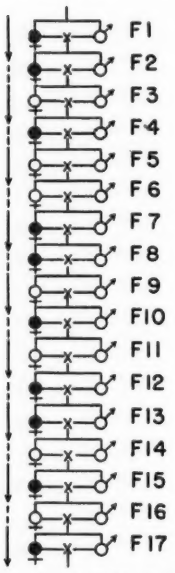


Fig. 3. The "skipping" of individual carriers (individuals who show no symptoms but transmit the disease) in the course of vertical transmission of mammary carcinoma in mice. Since transmission occurs from one individual to another of successive generations, the skipping of individual carriers results in the skipping of entire generations.

transmit it to other hosts, and yet never show any symptoms of disease. Thus, in its spread from one host to another, infantile paralysis, typhoid fever, as well as mouse mammary carcinoma, may skip one, two, or more intermediate hosts. Actually, the infectious agents do not "skip" the carriers; they pass through them, without causing any appreciable symptoms of disease.

Since, in the case of mouse mammary carcinoma, the transmission occurs between hosts of successive generations, an occasional skipping of a carrier would mean the skipping of an entire generation; skipping of two successive carriers would mean skipping of two successive generations (Fig. 3). It is clear, therefore, that the "vertical" pattern of transmission assures the tumor agent an unchallenged power to submerge for such long periods of time as to give the casual observer the impression of a final disappearance. After a few generations, the tumor may then reappear suddenly; for the incidental observer, however, who does not have at his disposal records of several previous generations, the apparently sudden development of a tumor may give the impression of "spontaneous" origin.

We do not yet know why some individuals may actually carry and spread the agents of diphtheria, typhoid fever, or infantile paralysis, for instance, but never show any appreciable symptoms of disease. We are more informed, however, about at least some of the reasons which may prevent a mouse, that actually carries and spreads the mammary carcinoma virus, from developing a tumor. A potentially cancerous mouse, of a tumor family, may have several successive litters and transmit the tumor agent through milk, to the next generation; and yet, the same animal may die from an intercurrent infection, such as pneumonia, a long time before it reaches the tumor age, i.e. before it has a chance to develop a tumor. Recent observations also suggest that mice actually carrying the agent may live their full life span without developing breast tumors, provided their caloric food intake is restricted. Thus, a simple reduction in calories, without alteration in the amount of dietary essentials, reduced the incidence of spontaneous mammary carcinomas in C_3H females from 100 to 12.5 per cent or less. This reduction in the incidence of spontaneous tumors could be accomplished by a caloric intake which, although restricted, was far from being a starvation diet (53, 58, 36). Many other factors, such as sexual life (number of pregnancies), crowding of cages (2), etc., are also of some importance in determining the early or late development of mammary tumors. Most of these factors are not yet fully understood.

THE LAW OF OBLIGATE COMMUNICABILITY IN MOUSE MAMMARY CARCINOMA

The fact remains unchanged, nevertheless, that mammary carcinoma of mice is transmitted from one generation to another; that frequently a generation or two are skipped; that many animals, actually carrying and spreading the tumor agent, never show any symptoms of cancer. Only accurate and complete records kept over the span of many successive generations allow the investigator to

follow the actually continuous, though at times inapparent, chain of transmission of the causative tumor agent. If complete records are on hand, the pattern of transmission becomes at once evident; it then becomes clear that each case of mammary carcinoma can in these animals be traced to another similar case of the same disease. The law of obligate communicability (Fig. 4) long established for other infectious diseases, becomes then evident also for mammary carcinoma of mice (33).

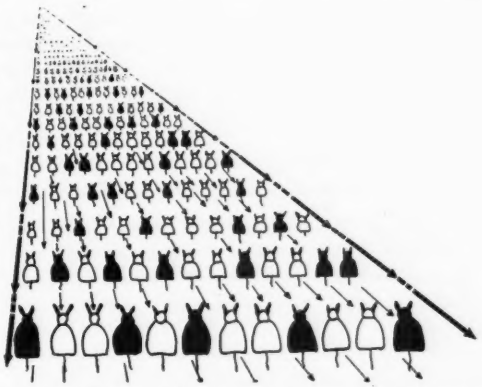


Fig. 4. The vertical epidemic of cancer. (1) This is *not* inheritance, but a *vertical* transmission of an extraneous *parasitic* agent. (2) The agent is communicable from one individual to another of *successive* generations. (3) Many carriers transmit the virus but never show any symptoms of disease.

THE TRANSMISSIBLE INACTIVE FORM OF THE TUMOR AGENT, AND ITS DELAYED ACTIVATION IN THE HOST

Among the many questions which immediately present themselves, one of the most striking is that concerning the very long interval of time which passes between the exposure of the host to the transmissible agent (early infancy), and the actual appearance of symptoms of the disease, i.e. the formation of the tumor.

It appears possible to assume that the invisible tumor agent is transmitted from one animal to another in some inactive form, and that it remains inactive and harmless, during most of the life span of its host. Usually at the end of the host's life cycle, conditions may develop which, at least in some instances, may prompt an activation of the hitherto inactive tumor agent. The conditions favoring such activation have not yet been fully determined, and are poorly understood; at least some of these conditions, however, are known, as for example old age, or certain hormonal stimulations.

Upon activation of the tumor agent, a new growth develops at the site of the activation, i.e. locally, in the cells where the agent was harbored, and where activation actually occurred. From then on, the activated agent causes the cells to multiply at the point of activation. The tumor then grows rapidly, infiltrating the surrounding tissues, not unlike any local infection; it may also spread through the lymphatic channels into either adjoining groups of lymph glands, or, apparently through migrating tumor cells, it may form distant metastases.

THE ACTIVATION OF TUMOR AGENT IS LOCAL

It is possible to assume that only a small fraction of the agent, which is harbored by the host, becomes at one time activated, forming a new growth and that the activation is thus a purely local phenomenon. The remaining inactive agent, harbored elsewhere by the same host, may not become activated at the same time. Thus, a host that bears a tumor (caused by an activated agent) may harbor, in addition, in other, apparently healthy tissues, the remaining inactive tumor agent. At a later date, however, should the host survive for a prolonged period of time, additional new activations of the tumor agent may occur at new sites, forming new primary tumors. This would explain the commonly observed fact that spontaneous mammary carcinomas may develop successively in several different mammary glands in a mouse. Conditions favoring the initial activation may either persist, or again develop, causing successive appearance of several similar tumors. The activation theory would perhaps explain why tumors that appear to develop only in middle aged or old animals, once they develop, will grow indiscriminately, upon transplantation, in either old or young hosts. Thus, it is not a resistance of the young animal to the tumor, but the lack of an *active* tumor agent that is responsi-

ble for the absence of spontaneous mammary carcinomas in youth and early adult age. Once activated, however, the tumor seems to be equally capable of growing, when transplanted, in susceptible hosts of any age (32).

THE VERTICALLY TRANSMITTED PARASITIC AGENTS IN INSECTS AND PLANTS

There exist many communicable diseases which are transmitted vertically, and which, in principle at least, follow the pattern observed in mammary carcinoma of mice. The Rocky Mountain spotted fever rickettsiae (49), or the tularemia organisms (41) (Fig. 5), for instance, are transmitted in the tick through the eggs of these insects from one generation to another, i.e. vertically. The "horizontal" transmission of these organisms, that is a transmission between insect-hosts belonging to the same generation, is possible when an intermediary host, such as man, for instance, intervenes. In the absence of a suitable intermediary host, however, only vertical transmission occurs. Many other communicable diseases of insects exist that are known to be transmitted from one generation to another, vertically (49, 41, 42, 27, 29), not unlike mammary carcinoma of mice.

Similar observations have been made on plants. Thus, it was observed that certain diseases of plants, caused by extraneous, filterable viruses, are transmitted from one plant to another through the seeds. An infected plant may grow next to a healthy one and yet no transmission of the disease will occur among hosts belonging to the same generation. However, the infected plant will transmit the virus through the seeds or, in the case of mosaic disease of the potato, through the tubers, to the next generation. The transmission through the seeds or through the tubers, from one generation to another, is essentially a "vertical" transmission of the parasitic agent, fundamentally similar to that observed in mammary carcinoma of mice (Fig. 6). The same is true for the mosaic disease of lettuce, tomatoes, or certain other plants (30, 38).

The vertically transmitted parasitic agents can readily escape detection, particularly when such parasites are invisible, and when they do not always cause symptoms of disease. The detection becomes somewhat easier in experiments conducted on hosts having a relatively short life span, and a rapid reproduction cycle; under such experimental conditions the actual host-to-host transmission of the pathogenic agents can be more readily followed by the human observer. Even in such instances, however, the difficulties are great, and great patience is required.

VERTICAL EPIDEMIC IS NOT TO BE CONFUSED WITH HEREDITY

At first sight, vertical transmission may be perhaps confused with inheritance. Upon observing a disease appearing successively in different descendants of the same family, a casual observer may be tempted to consider it to be caused by some inherited genetic factors. And yet, inheritance and vertical transmission are fundamentally different phenomena. A vertically transmitted mammary carcinoma is actually caused by a host-to-host transmission of an extraneous, acquired, parasitic agent. The same is true for mosaic disease of plants, or certain vertically transmitted virus diseases of insects.

Inheritance, on the other hand, is neither acquired, nor is it caused by extraneous, parasitic agents.

IMPORTANCE OF SUSCEPTIBILITY IN THE DEVELOPMENT OF MOUSE MAMMARY CARCINOMA AS COMPARED WITH OTHER COMMUNICABLE DISEASES

The proper susceptibility of the host to the disease-causing agent is obviously fundamental in the development of mammary carcinoma of mice. This factor, however, is equally important in other communicable diseases, since pathogenic micro-organisms or viruses can act only on susceptible hosts. Plague, for instance, is highly dangerous for man and certain rodents, but harmless for chickens. The susceptibility of man to plague is inherited; and yet, no one would state that plague, in man, is caused by (a) the plague bacillus and (b) inherited susceptibility of man; the plague bacillus only would be mentioned as the causative agent, since it goes without saying that this micro-organism will produce disease only in a susceptible host.

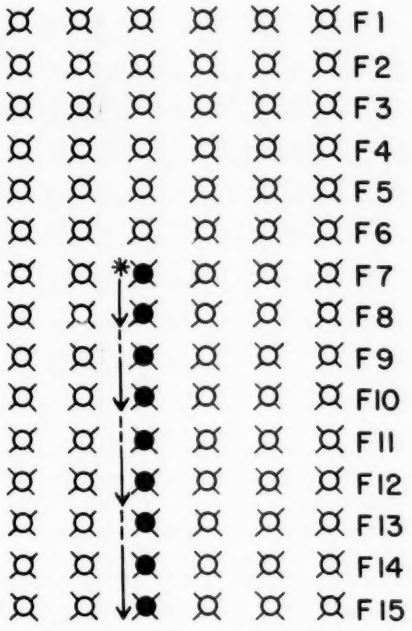


Fig. 5. Vertical transmission of tularemia in tick following exposure, that is, feeding on a host infected with tularemia.

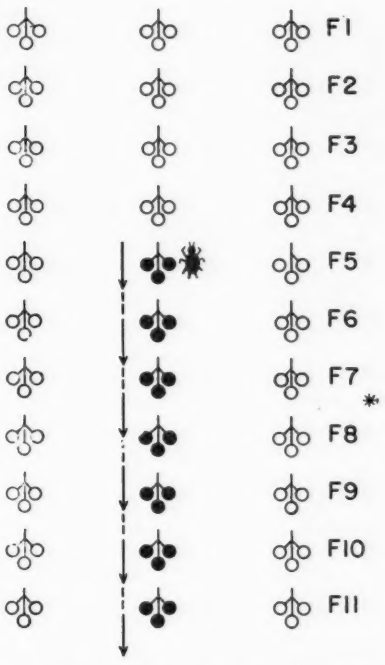


Fig. 6. Vertical transmission of mosaic virus in the potato following exposure. A plant louse (potato aphis) infected with mosaic virus fed on leaf of potato.

It is true that some mice are more, others less, susceptible to the tumor agent, and that such a susceptibility is inherited. This fact, however, would not surprise an epidemiologist. Thus, field mice are relatively resistant to streptococci or pneumococci, whereas albino mice are very susceptible to these organisms (28); by inbreeding of either susceptible or nonsusceptible parents, two different lines of mice were obtained by Webster, one showing 95 per cent mortality and the other only 5 per cent under the same conditions of exposure to the Bacillus enteritidis (57).

The importance of inherited susceptibility in the acquisition and development of mammary carcinoma should be viewed in its proper perspective, and should be neither overemphasized nor misinterpreted. The susceptibility of the host, which is essentially inherited, seems, at least in principle, no more important in the origin of mammary carcinoma than it is in the acquisition of diseases caused by various micro-organisms and viruses (33).

NO PEDIGREED INBREEDING NEEDED FOR TRANSMISSION OF MOUSE MAMMARY CARCINOMA

When the initial observations on vertical transmission of mammary carcinoma were made on mice, it appeared at first that genetic inbreeding is of paramount importance in such host-to-host passage of the tumor agent. It was later observed, however, that no pedigreed inbreeding is required for such a transmission, and that the promiscuous breeding, such as exists in nature, gives also the tumor agent an opportunity to pass from one host to another of successive generations.

Thus, middle aged mice that develop mammary carcinoma spontaneously can be found occasionally among the animals sold to clinical laboratories by dealers and known as "market mice." Such animals are, of course, of unknown genetic origin, being the offspring of promiscuous breeding. When such

tumor-bearing females were mated successively to several genetically unrelated males, numerous spontaneous mammary carcinomas developed among their offspring (24, 25); apparently, these mice transmitted the tumor agent to their progeny, even though they were far from following any rules of pedigreed inbreeding.

In another experiment, mice that were born to "market" albino mice of unknown ancestry, were foster nursed by female mice of the C_3H line whose milk was known to contain the tumor agent; as a result, 14 of 17 foster nursed females, i.e. 82 per cent developed mammary carcinomas upon reaching approximately 1 year of age (7). Eighteen sisters of these females were nursed, as controls, by their own albino mothers, and none of these died of cancer. These experiments were repeated, and confirmed in this laboratory (32). In our series, 23 albino females of unknown ancestry, obtained from a clinical laboratory, were transferred within 24 hours after birth for the purpose of foster nursing to female mice of the C_3H line (Fig. 7). Sixteen of these, i.e. 70 per cent developed carcinomas at the average age of 15 months (Fig. 8). No tumors were observed among the not fostered females. Thus, here again, the ingestion of the tumor agent in infancy resulted in the development of tumors in mice of unknown ancestry.

HORMONAL STIMULATION AND BREAST CANCER

When the initial observations were made suggesting that mammary carcinoma could be produced in male mice by either implanting ovaries, or injecting follicular hormones, it was thought, at first, that this was a cancer of "hormonal origin" (39). Only subsequent experiments have demonstrated that no amount of follicular hormone would produce mammary carcinomas in mice that do not carry the specific tumor agent (18, 40, 47, 54). Thus, in families of mice that apparently carry the tumor agent, i.e. in which the majority of females develop spontaneous mammary carcinomas, the male population remains free from these tumors, even though the males also carry the tumor agent. Such males will develop mammary carcinomas, however, if their mammary glands are stimulated by early, and potent injections of follicular hormone. On the other hand, similar application of the follicular hormone to male mice belonging to families free from the mammary carcinoma agent, i.e. to families whose females do not develop breast cancer, will not result in the development of tumors. If males of such tumor-free families, however, are foster nursed by females carrying the tumor agent, and then injected with follicular hormones, mammary tumors will develop.

It is now clear that mammary carcinoma is not caused by hormonal stimulation, but by the transmissible tumor agent. Obviously, the agent must act on susceptible hosts to produce symptoms of the disease; in addition to the general inherited susceptibility of the host, the agent apparently also requires active, and adequately stimulated mammary gland tissue in order to actually form a tumor. Repeated pregnancies, or injection of potent follicular hormones may in such cases prompt the development of tumors (4, 11), provided of course, that the specific tumor agent is harbored by the host.

The mammary carcinoma agent seems to have a discriminatory affinity for particular groups of cells (mammary glands) within the host. It is well to remember, however, that in this respect again the mammary carcinoma agent does not, in principle, differ from many other pathogenic viruses. To give an example, the infantile paralysis virus has a distinct affinity to certain cells of the spinal cord of man. Many other micro-organisms possess a limited affinity to certain groups of cells within a limited range of susceptible hosts.

Hormonal stimuli may also distinctly influence the susceptibility of the host to various communicable diseases; thus, males have long been observed to be more susceptible than females to many infectious diseases in both human and animal pathology (28). On the other hand, the hormonal stimuli may in certain instances increase the resistance of the host to parasitic agents; Tinea tonsurans, for example, occurs in childhood, but does not usually affect sexually mature individuals (45).

Thus, hormonal stimulation, like inherited susceptibility, may, at first sight perhaps, ap-

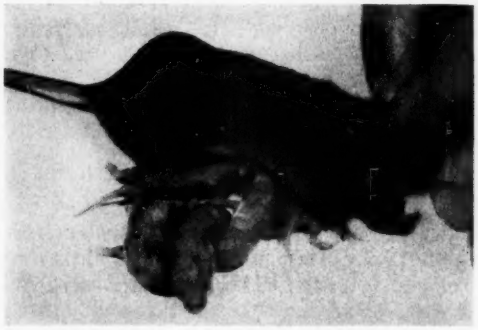


Fig. 7. A newly born litter of albino "market" mice of unknown ancestry was foster nursed by a female of the C3H line whose milk contained the tumor agent.

Fig. 8. One of the majority, 70 per cent, of the foster nursed albino females that developed spontaneous mammary carcinomas upon reaching 1½ years of age.

pear to be of unusual importance in the origin of mammary carcinoma of mice, and that of cancer in general. Upon reviewing these observations on a broader basis, however, it becomes apparent that inherited susceptibility, and hormonal stimulation, are both also essential in the development of various communicable diseases.

THE IMPLICATIONS OF THE NEW APPROACH TO THE PROBLEM OF CANCER

The theoretical implications of the observations discussed are considerable. To begin with, it appears difficult to consider that the mouse mammary carcinoma develops "spontaneously." Breast cancer in mice appears to be no more "spontaneous" than a case of tuberculosis or typhoid fever. Provided that sufficient records are on hand, each case of tuberculosis, or typhoid fever, could obviously be traced to another case of similar disease, the conditions being caused by specific, transmissible agents. The same appears to be true for mammary carcinoma of mice. It is well to remember that only a generation or two ago many physicians thought that tuberculosis, typhoid fever, or for that matter a number of other communicable diseases, were of "spontaneous" origin, and resulted from various different internal and external causes. As late as 1885 typhoid fever and diphtheria were believed to originate *de novo* in filthy surroundings (44). The discussion on "spontaneous tuberculous degeneration" (43) printed in the *Bulletin* of the French Academy of Medicine in 1867 may appear amusing to a contemporary physician; in 1866, however, the suggestion advanced by Villemin (55) that tuberculosis is not a "spontaneous" disease, but is caused by a transmissible, parasitic agent, did not gain much support among his contemporary colleagues. It took years to demonstrate the law of obligate communicability for all infectious diseases.

We do not know at the present time of any communicable disease that would develop *de novo*. There is no convincing evidence to support the idea of spontaneous generation of any, no matter how small, parasitic agents. Invisible viruses are much more difficult to detect than the larger microbes. If they are harbored by a host without causing symptoms of disease, they may remain undetected without attracting attention of the most careful observer. They may then pass to other hosts and at a later date cause symptoms of disease so unexpectedly as to give the impression of being produced *de novo* or by some obscure process of mutation.

One of the most interesting features of the epidemiology of mouse mammary carcinoma is its "vertical transmission," i.e. the passage of the virus from one generation to another. In the case of many common communicable diseases, the chain of infection spreads among individuals of the same generation, i.e. "horizontally"; as a result, many consecutive cases of transmission of the disease from one in-

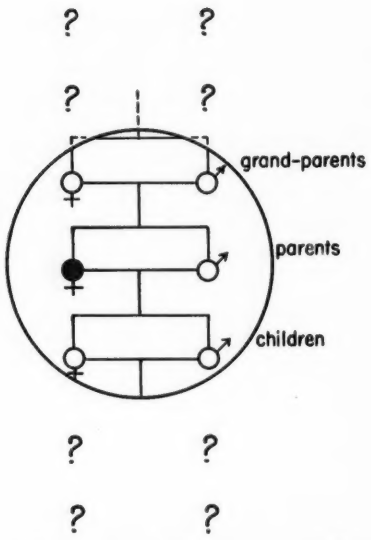


Fig. 9. Cancer *appears* to be a spontaneous disease. In most instances information available is limited to three generations, that is to the individual concerned, and the next succeeding and preceding generations.

dividual to another occur within a comparatively short time, and the whole picture of a "communicable" disease is clearly discernible to any individual observer. In the case of tumors, however, the epidemiological picture is fundamentally different. Thus, in the case of mammary carcinoma at least, the pathogenic agent is transmitted from one individual to another of successive generations; many of the individual carriers may actually harbor and transmit the virus but never show any symptoms of disease.

Theoretically, it is possible to assume that breast cancer could kill the great-grandmother, then skip the grandmother, mother, and so forth, only to reappear perhaps in the great-granddaughter in its usual form of a typical breast carcinoma. In reality, the tumor agent does not skip any of the individuals through which it passes. They all carry the tumor agent, though many of them never show any symptoms of tumors. Because, however, the mammary carcinoma agent can cause no symptoms, and because it is transmitted vertically, it may actually submerge for one, two, or more generations of hosts disappearing entirely from the sight of the most patient observer (Figs. 9 and 10). Years, and in man perhaps even a century or two, may sometimes elapse between cases of disease that have been caused by transmission of the same pathogenic agents (34, 35).

"SPONTANEOUS GENERATION" AND MOUSE MAMMARY CARCINOMA

The law of obligate communicability is at the present time so generally accepted that no one would venture to state that he observed a case of "spontaneous tuberculosis not caused by bacillus tuberculosis" even though here and there cases of unquestionable clinical tuberculosis might have been observed with apparent difficulty in demonstrating the presence of the specific pathogenic agent. In the case of mammary carcinoma of mice, however, it appears, to some authors, at least, perfectly plausible to state that a case of mouse mammary carcinoma has been observed which has not been caused by a transmissible milk factor (i.e. tumor virus) because no presence of such a tumor agent could be demonstrated in the particular case by the investigators (37). Thus, some investigators still believe that certain mouse mammary cancers are caused by a specific, transmissible agent while others, clinically identical tumors developed *de novo* (16), and are of "spontaneous" origin. Actually, however, the concept of "spontaneity" of mouse mammary carcinoma seems untenable in view of the experimental evidence suggesting that breast cancer of mice is communicable from generation to generation, and that its appearance can be effectively prevented by isolating the potentially cancerous mothers from their newly born progeny.

HUMAN TUMORS

The "vertical" transmission of mammary carcinoma in mice, from one host to another, through a filterable agent contained in the milk of nursing mothers has been established experimentally beyond any reasonable doubt. The question arises immediately whether this origin of breast cancer is limited to mice or is valid also for other species of mammals including man. In addition, the question also arises whether tumors other than mammary

carcinoma have a fundamentally different etiology.

No exact answer is possible at the present time to either of these important questions. Until more information on experimental cancer is obtained, only a tentative assumption based on theoretical considerations could be ventured. It is possible to assume, however, that mammary carcinoma of mice does not represent a form of cancer different from breast cancer in other mammals. If this assumption is correct, the law of obligate communicability may in the future be established also for breast cancer in such animals as rats, rabbits, or dogs, and perhaps also in women.

PREVENTING HUMAN BREAST CANCER BY ARTIFICIAL FEEDING?

Should such a possibility materialize, the eradication of human breast cancer may become feasible by the simple method of artificial feeding of infants born to mothers having a family history of tumors (17, 33, 34, 35).

There is at the present time no other way of suspecting the presence of the tumor agent in the milk of a nursing female mouse except by checking her family record for the occurrence of tumors. A female mouse whose milk contains the tumor agent is in perfect health at the time of nursing; she will develop mammary carcinoma upon reaching middle age, if she develops a tumor at all; she may die before she reaches the tumor age; on the other hand, she may live her normal life span and yet never develop a tumor (although she carries and transmits the tumor agent) if her diet is restricted (36, 53, 58) so as to cut her caloric intake by 30 to 50 per cent. The only way to determine whether she carries and transmits the tumor agent is to check her family record. Her mother might have died without a tumor, as well as her grandmother, but perhaps a sister of her mother, or her great-grandmother for instance, developed a mammary carcinoma.

The same may be true for human breast cancer. Thus, a history of breast cancer in the family of a nursing and apparently healthy mother may indicate the presence of a tumor agent in her milk. Since no more than a few hours of breast feeding may suffice to transfer the tumor factor, the conclusion seems justified that breast feeding in such instances should be abandoned *from birth*. It might suffice to omit breast nursing for one single generation in order to interrupt the flow of the virus. Breast feeding could then be resumed in the succeeding generations.

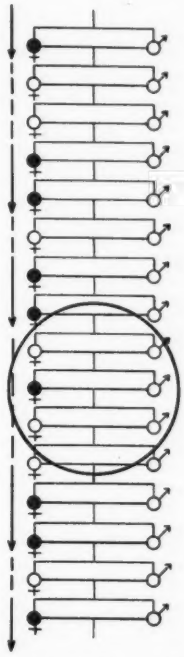


Fig. 10. The vertical transmission of cancer becomes discernible only when records are available covering a sufficient number of generations.

Since the tumor agent does not appear to resist heating to 61 degrees C. for 30 minutes (7, 8), feeding of pasteurized human milk (56) should also be considered.

THE ORIGIN OF TUMORS OTHER THAN MAMMARY CARCINOMA

The second important question requiring clarification is that dealing with the possible origin of tumors other than mammary carcinomas. Except for some particular tumors of dogs, chickens, frogs, or rabbits, there is, in the great majority of instances, no evidence to suggest that the various sarcomas and carcinomas that develop for obscure reasons in

different organs of animals and man, are caused by transmissible agents. And yet, it is difficult not to be impressed by the fact, that in various species of hosts, such as mice, rats, rabbits, chickens, fish, cattle, etc. families have been observed with an incidence of either tumors, or allied diseases, such as leucemia, substantially higher than that of the average population. Also in man, it is rather difficult to ignore the often striking frequency of malignant tumors developing in members of families of patients suffering from cancer (33). This observation has been made so often that a positive, for cancer, family record is actually considered to be of diagnostic value (22).

In principle it appears possible, perhaps even reasonable, to assume, that mammary carcinoma of mice does not represent a form of cancer fundamentally different from at least some of the other malignant neoplasms. If this assumption is correct, the law of obligate communicability may in the future become established also for tumors other than breast cancer (33). Such an assumption would not necessarily imply that milk only should be considered as means of natural transmission of a causative tumor agent. Tumors are not limited to mammals, and it would only be logical to assume that means of transmission other than milk also exist, should such transmission occur at all.

A WORKING HYPOTHESIS

The observations discussed above are as yet insufficient to draw any generalized conclusions. It is possible, nevertheless, to advance a working hypothesis as to the origin of at least certain malignant neoplasms in animals, and also in man.

There may exist a group of transmissible agents causing tumors in animals and in man; these agents would be so small as to be invisible under an ordinary, optical microscope; they would possess many of the characteristics of pathogenic viruses. These agents would be fundamentally similar in certain features of their behavior. Thus, they would attack certain groups of cells within certain hosts, live and multiply in such cells; as a rule, these tumor agents would be frugal and moderate in their requirements, and would not apparently injure the host. For obscure reasons, however, the pathogenicity of the agent may sometimes change during the latter part of the life of the host, and a tumor would then develop, usually sealing the fate of the host, i.e. growing progressively, and, if not treated, killing the host. The survival of the agent would have been in the meantime secured, however, by transmission to another host occurring as a rule prior to the appearance of symptoms of a tumor in the transmitting individual.

One of the most striking features of the pattern of natural transmission of these agents would be their faculty to pass "vertically," from one host to another of successive generations. The generation-to-generation transmission, with occasional "skipping" of intermediate carriers, i.e. with skipping of generations, would make the task of tracing the epidemiological course of the tumor agent extremely difficult, and time consuming. Although the tumors would in principle belong to the general group of "communicable" disease, transmission would occur as a rule among hosts of successive generations.

The agent would appear to be able to attack new hosts efficiently in either their embryonic stage, or in their infancy. A long, asymptomatic phase of the disease would then follow, during which the host would transmit the agent to the succeeding generation. The activation of the hitherto latent agent in the transmitting host would then follow, though it would not always have to occur. The activation of the tumor agent could be prompted by a number of either general or local, nonspecific, factors, such as those related to aging, by hormonal stimuli or metabolic disturbances, by exposure to irradiation, or to certain systemic poisons, etc. In some instances, the activation of the agent could be prevented by either hormonal influences, by a restricted food intake, or perhaps by some other as yet obscure factors.

Although fundamentally similar in certain features of their behavior, these tumor agents would be individually distinct, causing different malignant neoplasms, not unlike the array of rickettsial micro-organisms responsible for the various forms of typhus. If this assumption is correct, the number of animals,

and people, with demonstrable tumors would represent only a fraction of those actually carrying the disease (33).

SUMMARY AND CONCLUSIONS

1. Mammary carcinoma of mice, a disease essentially similar to breast cancer of women, is caused by a filterable agent, which is transmitted from one generation to another through the milk of nursing females. This agent can be destroyed by heating to 61 degrees C. for 30 minutes, i.e. it would not resist pasteurization. The agent has antigenic properties, and can be neutralized in vitro by a specific immune serum.

2. The development of mammary carcinoma in mice can be prevented by the simple method of isolating the newly born animals from their potentially cancerous mothers, and by transferring them for the purpose of nursing to female mice whose milk is free from the tumor agent.

3. Mice of either pedigreed inbred lines, or offspring of promiscuous breeding can be infected in infancy by ingesting the mammary carcinoma agent. They remain then in perfect health, through their early adult life. Upon reaching one to one and a half years of age, however, they develop mammary carcinomas. In the meantime, they have transferred the tumor agent to their own offspring, and have thus assured the continuation of the disease in the next group of hosts.

4. Thus, a female mouse which is nursing, is in perfect health at the time she is actually infecting her offspring with the tumor agent. The only indication suggesting that she harbors and discharges the tumor virus is her record showing that mammary carcinomas developed in her female ancestors.

5. These observations suggest that mammary carcinoma is not a "spontaneous" disease. The law of obligate communicability long established for other infectious diseases appears to be valid also for breast cancer of mice.

6. The natural transmission of mammary carcinoma agent occurs only from one host to another of successive generations. The term "vertical epidemic" has been suggested for this type of transmission of pathogenic agents. Many parasites of plants and insects follow this pattern of transmission, passing from one host to another through either seeds or ova. "Vertical epidemic," however, should not be confused with inheritance; these are two fundamentally different phenomena.

7. The possibility is discussed that mammary cancer of other mammals, including man, may also be caused by agents similar to that responsible for mouse mammary carcinoma. If this assumption is correct, women who have a family history of tumors should not nurse their babies; artificial feeding, or feeding with pasteurized human milk should be substituted. This simple preventive measure may interrupt the flow of the virus and eradicate human breast cancer within one generation; breast nursing could then be resumed.

8. It is possible to assume that mammary carcinoma of mice is not exceptional in its etiology, but represents a condition essentially similar to other neoplasms. If this is true, other malignant tumors may eventually prove to be caused by transmissible agents. It would then be logical to assume, however, that milk is not the only means of transmission of such agents; transfer through ova, and otherwise, would also have to be considered.

9. The hypothesis is advanced that there exists a group of viruses causing various malignant tumors in animals and in man. These viruses would live in close association with normal cells, be usually frugal and moderate in their requirements, and cause no symptoms of disease. They would be transmitted among hosts of successive generations i.e. vertically. In most instances the carriers would never show any symptoms of tumors. Occasionally, however, prompted by obscure factors, the tumor virus would become activated, causing a local new growth.

10. Because of the existence of many asymptomatic carriers, however, and the occasional "skipping" of generations, it would only become possible actually to trace the host-to-host passage of the "vertically" transmitted tumor agents when accurate and complete mortality records are on hand covering the span of many successive generations.

11. If this hypothesis is correct it would logically follow that, should such records ever

become available, each case of human cancer could then be traced to another case of a malignant tumor in one of the patient's ancestors.

12. The comparatively high incidence of tumors in families of patients suffering from cancer, long recognized by various observers, would thus assume a more than incidental significance. Accordingly, a family history of cancer should perhaps be more appreciated from the point of view of its possible diagnostic value, particularly in patients with symptoms difficult to be properly classified.

REFERENCES

1. Andervont, H.B. J. Nat. Cancer Inst., 1940, 1: 147-153.
2. Ibid., 1944, 4: 579-581.
3. Ibid., 1945, 5: 397-401.
4. Andervont, H.B., and McEleney, W.J. Pub. Health Rep., Wash., 1938, 53: 777-783.
5. Idem. J. Nat. Cancer Inst., 1941, 1: 737-744.
6. Andervont, H. B., Shimkin, M. B., and Bryan, W. R. J. Nat. Cancer Inst., 1942, 3: 309-318.
7. Andervont, H. B., and Bryan, W. R. J. Nat. Cancer Inst., 1944, 5: 143-149.
8. Barnum, C. P., Ball, Z. B., Bittner, J. J., and Visscher, M. B. Science, 1944, 100: 575-576.
9. Bittner, J. J. Am. J. Cancer, 1935, 25: 614-620.
10. Idem. Science, 1936, 84: 162.
11. Idem. Pub. Health Rep., Wash., 1939, 54: 380-392.
12. Ibid., 1939, 54: 1827-1831.
13. Idem. Proc. Soc. Exp. Biol., N.Y., 1940, 45: 805-810.
14. Idem. J. Nat. Cancer Inst., 1940, 1: 155-168.
15. Idem. Science, 1941, 93: 527-528.
16. Idem. Cancer Res., 1941, 1: 113-114.
17. Idem. Tr. Coll. Physicians Philadelphia, 1941, 9: 129-143.
18. Idem. Cancer Res., 1941, 1: 290-292.
19. Idem. Science, 1942, 95: 462-463.
20. Idem. A.A.A.S. Res., Conf. on Cancer, 1944, pp. 63-96.
21. Bittner, J. J., Evans, C. A., and Green, R. G. Science, 1945, 101: 95-97.
22. Cutler, M., Buschke, F., and Cantril, S. T. Cancer, Its Diagnosis and Treatment. Philadelphia: W. B. Saunders, 1939.
23. Dmochowski, L. Brit. J. Exp. Path., 1945, 26: 192-197.
24. Dobrovolskaia-Zavadskaia, N. C. rend. Soc. biol., 1930, 103: 994-996.
25. Ibid., 1931, 107: 466-469.
26. Idem. Radiology, 1932, 18: 805-808.
27. Francis, E. Pub. Health Rep., Wash., 1938, 53: 2220-2241.
28. Gay, F. P., and associates. Agents of Disease and Host Resistance. Baltimore: Thomas, 1935.
29. Glaser, R. W. In: Filterable Viruses. Edited by T. M. Rivers. Pp. 279-326. Baltimore: Williams & Wilkins Co., 1928.
30. Gratia, A. In: Les ultravirus des maladies humaines by C. Levaditi and P. Lepine. Pp. 109-157. Paris: Maloine, 1938.
31. Green, R. G., Moosely, M. M., and Bittner, J. J. Proc. Soc. Exp. Biol., N. Y., 1946, 61: 115-117.
32 Gross, L. Unpublished experiments.
33. Idem. Cancer Res., 1944, 4: 293-303.
34. Idem. N. York State J. M., 1946, 46: 172-176.
35. Ibid., 1947, 47: 866-867.
36. Huseby, R. A., Zelda, B., Ball, M. S., and Visscher, M. B. Cancer Res., 1945, 5: 40-46.
37. Kirschbaum, A., and Bittner, J. J. Proc. Soc. Exp. Biol., N. Y., 1945, 58: 18-19.
38. Kunkel, L. O. In: Filterable Viruses. Pp. 335-363. Edited by T. M. Rivers. Baltimore: The Williams and Wilkins Co., 1928.
39. Lacassagne, A. C. rend. Acad. sc., 1932, 195: 630-632.
40. Morris, H. P., and Thompson, J. W. J. Nat. Cancer Inst., 1940, 1: 395-396.
41. Parker, R. R., and Spencer, R. R. Pub. Health Rep., Wash., 1926, 41: 1403-1407.
42. Pasteur, L. C. rend. Acad. sc., 1865, 61: 506-512.
43. Pidoux. Bull. Acad. méd., Par., 1867, 32: 1268-1301.
44. Rivers, T. M. Bull. N. York Acad. M., 1938, 14: 383-397.
45. Sabouraud, R. Diagnostic et traitement des affections du cuir chevelu. Paris: Masson et Cie, 1932.
46. Shimkin, M. B., and Andervont, H. B. J. Nat. Cancer Inst., 1941, 1: 599-605.
47. Ibid., 1942, 2: 611-622.
48. Slye, M. Am. J. Cancer, 1931, 15: 1361-1386.
49. Spencer, R. R., and Parker, R. R. Pub. Health Rep., Wash., 1924, 39: 3027-3040.
50. Strong, L. C. Genetics, 1935, 20: 586-591.
51. Idem. J. Hered., 1936, 27: 21-24.
52. Idem. Cancer Res., 1942, 2: 531-539.
53. Tannenbaum, A. Cancer Res., 1942, 2: 460-467.
54. Twombly, G. H. Proc. Soc. Exp. Biol., N. Y., 1940, 44: 617.
55. Villemin, J. A. Bull. Acad. méd. Par., 1866, 31: 211-216.
56. Watson, M. L. Am. J. Nurs., 1941, 41: 672-674.
57. Webster, L. T. Medicine, 1932, 11: 321-344.
58. White, F. R., White, J., Mider, G. B., Kelly, M. G., and Heston, W. E. J. Nat. Cancer Inst., 1945, 5: 43-48.
59. Woolley, D. W., Law, L. W., and Little, C. C. Cancer Res., 1941, 1: 955.

SUBMUCOUS LIPOMA OF THE COLON

CHARLES W. MAYO, M.D., F.A.C.S., and DONALD F. GRIESS, M.D., Rochester, Minnesota

MANY reviews and individual reports of cases of submucous lipoma of the colon have appeared in the literature since Bauer, in 1757, reported the spontaneous elimination of a lipoma, probably from the colon. A recent contribution to the subject is that of Pack and Booher, who stated that 153 cases of submucous lipoma of the colon had been reported in the literature to the time of completion of their paper.

The purpose of this study is to add to this number 19 cases of submucous lipoma of the large intestine in which operation has been performed at the Mayo Clinic from January 1, 1936, through December, 1947, and also to review briefly the salient features of symptomatology, situation, and surgical procedures performed for the condition.

Comfort and Pemberton and McCormack reported 24 cases of submucous lipoma of the large intestine from the clinic. These, together with the 19 cases reported in this paper, make a total of 43 cases in which operation has been performed for this particular condition at the Mayo Clinic up to and through the year 1947.

Lipomas of the colon occasionally are found on routine necropsies; these growths are relatively small and asymptomatic and since they are incidental findings they are only of academic importance.

REPORT OF CASES

CASE 1. An unmarried woman, aged 50 years, came to the Mayo Clinic on October 31, 1935, because of attacks of pain in the right side. The attacks had occurred intermittently for 12 years, the last one a week before admission. Examination disclosed a fibroid tumor and retroversion of the uterus. Total hysterectomy, bilateral salpingo-oophorectomy and appendectomy were performed on November 2, 1935. Convalescence was uneventful and the patient was dismissed on November 25, 1935.

On February 10, 1936, she returned because of pain in the epigastric region which she had experienced first shortly after the previous operation and which had increased steadily in severity. She also had had several attacks of mild intestinal obstruction. Physical examination revealed extreme tenderness and definite muscular rigidity in the right portion of the epigastrium. Roentgenologic examination of the colon revealed cecocolic intussusception, the cause of which could not be determined at the time.

Qn March 14, an exploratory laparotomy disclosed a lipoma of the cecum which had caused intussusception and partial obstruction of the intestine. Because the peritoneum in the ileocecal region was thickened and it was thought that the lesion might be malignant, about 3 inches (7.6 cm.) of the ileum, the cecum, the ascending colon and several inches of the transverse colon were excised and the continuity of the intestine was re-established by side-to-side anastomosis. An ileac stoma was established but this was closed at a later date. The pathologist reported that the tumor was a submucous lipoma which measured 6 by 5 by 4 centimeters. The surface of the tumor was ulcerated. When the patient was last heard from, she was in good health.

CASE 2. A married woman, aged 58 years, came to the clinic on October 18, 1937. In February, 1937, she first had noticed a mild burning pain in the right upper quadrant of the abdomen which had not been related to the ingestion of food. In August, 1937, roentgenologic examination had disclosed a filling defect in the first part of the transverse colon and in October, 1937, roentgenologic examination had disclosed a polypoid tumor in the first part of the transverse colon. She had not had any diarrhea, constipation, or change in bowel habit. Her stools had not contained any mucus or blood.

Physical examination revealed some tenderness in the right side of the abdomen. Proctoscopic examination did not reveal any abnormality. Roentgenologic examination of the colon revealed some changes in the cecum and ascending colon which were suggestive of amebic colitis. Therefore, treatment for amebiasis was instituted. Roentgenologic examination a week later revealed a local inflammatory lesion in the cecum. Hospitalization and treatment were advised. A subsequent roentgenogram revealed a polypoid lesion which was thought to be a lipoma situated in the transverse colon, near the hepatic flexure.

At laparotomy on November 12, 1937, the last 6 inches (15.2 cm.) of the ileum, the ascending colon, and the transverse colon were found to be slightly thickened. This thickening was thought to be due to amebic colitis. A tumor was found in the hepatic flexure of the colon and it was removed through a transverse incision in the colon. The pathologist reported that the tumor was a submucous lipoma; it

From the Division of Surgery, Mayo Clinic and Mayo Foundation.

measured 2 by 2 by 0.5 centimeters. The patient had an uneventful recovery. In a letter received from her 4 years later she did not complain of any difficulty.

CASE 3. A married woman, aged 43 years, came to the clinic on April 3, 1939, because of gall bladder colic. Her appendix and a cyst of the right ovary had been removed in 1916. A roentgenologic diagnosis of gallstones had been made in 1938. Hemorrhoids, with occasional bleeding and pruritus, had been present for many years. Proctoscopic examination had not been made.

Physical examination revealed an elongated mass, apparently of the colon, in the right lower quadrant of the abdomen. Roentgenologic examination disclosed that the gall bladder was not functioning in a normal manner. Roentgenologic examination of the large intestine was not made.

On April 6, 1939, exploratory laparotomy revealed a pedunculated tumor which projected into the lumen of the ascending colon. Because there was considerable inflammation of the surrounding tissues and since it was felt that the lesion might be malignant, about 4 inches (10 cm.) of the terminal portion of the ileum, the cecum, the ascending colon, and about half of the transverse colon were excised. The continuity of the intestine was re-established by side-to-side anastomosis. An enterostomy tube was inserted in the ileum at a point about 5 inches (12.7 cm.) above the line of anastomosis. The gall bladder also was removed. The pathologist reported that the tumor was a pedunculated lipoma of the cecum about 5 centimeters in diameter. The overlying mucosa was covered by an ulcer which was about 4 centimeters in diameter. The muscular coat of the surrounding intestine had undergone hypertrophy. The patient made an uneventful recovery.

CASE 4. A man, aged 52 years, came to the clinic on August 26, 1940, because of arthritis and the presence of blood in the stools. The small joints were swollen and tenderness was present over most of the joints. Examination of the abdomen did not disclose any abnormality. Proctoscopic examination disclosed external and internal hemorrhoids, grade 1 (on the basis of 1 to 4). Roentgenologic examination of the colon revealed diverticulosis and a polypoid tumor in the midportion of the descending colon.

At laparotomy on September 5, 1940 the descending colon and the first portion of the sigmoid flexure were found to be bound down rather tightly to the posterior portion of the abdominal wall because there was practically no mesentery. A soft nodule could be palpated in the descending colon. The colon was opened and the tumor was removed by dissection. The pathologist reported that the tumor was a submucous lipoma of the descending colon, 2.5 centimeters in diameter. The operative wound became infected but the patient recovered in a month.

CASE 5. A man, aged 50 years, came to the clinic on September 6, 1940, and stated that for the past 15 years he had had attacks of generalized, shifting, transient abdominal pain that had not been associated with nausea or vomiting and had not given evidence of any symptoms referable to the intestinal tract. The attacks had occurred once or twice a year and had lasted from 1 to 3 days. He had found that a bland type of diet would prevent the attacks. The patient also complained of pain in the epigastrium and in the left upper quadrant of the abdomen which was relieved by alkalies and milk.

Physical examination did not reveal any abnormality. Proctoscopic examination disclosed internal and external hemorrhoids. Roentgenologic examination of the stomach did not disclose any abnormality. A similar examination of the gall bladder revealed that this organ contained a calculus but that it was functioning normally. Roentgenologic examination of the colon disclosed a nonsessile polypoid tumor which was believed to be situated in the descending colon near its junction with the sigmoid flexure. The roentgenologist expressed the opinion that the tumor might be a lipoma.

Exploratory operation was performed on September 14, 1940. The tumor was found to be situated at the junction of the descending colon and sigmoid flexure. It was removed through a transverse incision in the colon. The pathologist reported that the tumor was a submucous lipoma of the sigmoid flexure, 2 centimeters in diameter.

The patient was in good condition when he was dismissed on October 7, 1940. In a letter dated November 22, 1940, he stated that he was in good health.

CASE 6. A man, aged 43 years, came to this clinic on September 5, 1941. About a year previously, he had begun to have attacks of cramping pain in the right upper quadrant of the abdomen. These attacks had occurred about once a week, had lasted from 1 to 3 minutes, and then had terminated suddenly. Although they had occurred at almost any time, they had had a tendency to start after meals. Four months before the patient came to the clinic, the frequency of the attacks had increased so that they had been present every day and had lasted about an hour during which the pain occurred at intervals of 2 to 4 minutes. The pain sometimes had awakened the patient at night and it sometimes had been present every half hour during the day. It was relieved by a bowel movement or by the passage of flatus. It usually was localized in the right upper quadrant of the abdomen but it sometimes extended to the left scrotal region. There had not been any diarrhea and the patient never had seen any blood in the stools.

Physical examination revealed a tender, movable mass in the right upper quadrant of the abdomen. Roentgenologic examination disclosed ileocolic intussusception. The intussusception first was observed in the middle of the transverse colon but in the course of the examination it was reduced as far as the hepatic flexure. At the completion of this part of the examination, the intussusception involved only the ileum and cecum. The roentgenologist reported

that there probably was a tumor or Meckel's diverticulum in the distal portion of the ileum.

On September 10, 1941, an exploratory laparotomy revealed intussusception of the cecum and ascending colon into the transverse colon. A tumor appeared to be attached to the first portion of the ascending colon by a thick pedicle. Because of the redundancy caused by repeated intussusception, about 4 inches (10 cm.) of the terminal portion of the ileum, the cecum and the ascending colon were excised. The continuity of the intestine was re-established by end-to-end anastomosis. The pathologist reported that the tumor was an ulcerating submucous lipoma of the cecum. It measured 6.5 by 5 by 5 centimeters and was situated opposite the ileocecal valve. In June, 1943, the patient reported that he was in good health.

CASE 7. A married woman, aged 48 years, registered on February 2, 1942, because of recurring attacks of colicky cramp which had been present for 4 months. The pain was situated in the right half of the abdomen and extended to the lower part of the right side of the thorax. It was not related to the ingestion of food or fluids but occurred in regular rhythm and kept her up at night; it lasted from 2 to 5 minutes and then disappeared for several minutes. It was relieved by bowel movements. In the past 4 months the number of bowel movements had increased from one to two a day and the stools were softer than they had been previously. The patient was nauseated and belched frequently. There was no blood in the stools.

Physical examination disclosed tenderness in the right upper quadrant of the abdomen. Proctoscopic examination disclosed small external and internal hemorrhoids. Roentgenologic examination of the colon disclosed a polypoid tumor about 5 centimeters in diameter which appeared to be attached to the lateral wall of the first part of the ascending colon by a pedicle. When the roentgenologic examination of the colon was started, the ascending colon was found to be invaginated into the transverse colon as far as the midportion of this segment.

Laparotomy was performed on February 7, 1942. A tumor about the size of a hen's egg was found in the ascending colon. Although the tumor appeared to be benign, it had caused the terminal portion of the ileum, the cecum and the ascending colon to become invaginated into the transverse colon as far as the midportion of this segment. The last 3½ inches (8.9 cm.) of the ileum, the cecum and the ascending colon were excised and the continuity of the intestine was re-established by end-to-end anastomosis. The operation was completed in a single stage. The pathologist reported that the tumor was a submucous lipoma of ascending colon which measured 5 by 5 by 4 centimeters. An ulcer, 3.5 centimeters in diameter, was found on the overlying mucosa. The patient made an uneventful recovery.

CASE 8. A man, aged 53 years, came to the clinic on January 25, 1943, because of abdominal cramps and diarrhea which had been present for 3 weeks. He also had discovered a painful mass in the left lower part of the abdomen. He had lost 10 pounds (4.5 kgm.) in the previous 6 months and had had occasional attacks of gaseous distention which had been relieved by the passage of flatus. Two weeks before admission he had had an attack of diarrhea and had noticed blood in the stools.

Physical examination revealed a fixed, slightly tender mass in the sigmoid flexure just above the brim of the pelvis. This mass was about 12 centimeters long. Proctoscopic examination revealed hemorrhoids. Roentgenologic examination disclosed a polypoid lesion of the descending colon at the level of the crest of the ilium. It was felt that the lesion probably was a carcinoma.

On January 29, 1943, exploratory laparotomy revealed a lesion in the descending colon just below the splenic flexure. The involved segment of the colon was thickened and congested; its appearance suggested intussusception or intestinal obstruction. The colon was exteriorized over a three-bladed clamp and about half of the transverse colon and most of the descending colon were excised. The pathologist reported that the tumor was a submucous lipoma of the descending colon which measured 4 by 3 by 2 centimeters and had caused intussusception into the sigmoid flexure. An ulcer which measured 3 by 2 centimeters was present on the surface of the tumor. The colonic stoma was closed on March 9, 1943.

The patient returned to the clinic for examination of his right knee on June 11, 1946, and at that time he did not have any symptoms referable to the intestinal tract.

CASE 9. A married woman, aged 46 years, came to the clinic on April 7, 1943. She had undergone appendectomy in 1919. Three years before admission, pain had developed in the epigastrium and had extended to the right lower quadrant of the abdomen. It had been aggravated by jolting and had been rather constant until a regimen for cholecystic disease had caused it to disappear. However, 2 months before she came to the clinic she again experienced epigastric pain which extended to the entire right side of the abdomen; it was a dull type of pain which usually occurred before meals but sometimes lasted for 24 hours. She complained of gaseous distention of the stomach which was aggravated by the ingestion of fried foods and was relieved by belching. She passed considerable flatus with her bowel movements. She did not give any history of pain in the right shoulder, of jaundice, acholic stools, nausea, or vomiting.

Physical examination revealed epigastric tenderness and an elongated mass in the right upper and lower quadrants of the abdomen. Mass extended upward to a point just above the umbilicus; it was tender, moved with respiration and had the consistency of rubber. Roentgenologic examination of the colon revealed a polypoid lesion of the cecum which was about 5 centimeters in diameter. Intussusception was found in the region of the hepatic flexure of the colon but the invagination was reduced easily

by manipulation while the opaque enema was being administered. Roentgenologic examination of the stomach and gall bladder did not disclose any abnormality of these organs.

April 13, 1943, exploratory laparotomy revealed a tumor which appeared to be situated in the ascending colon, near the cecum, and which had caused intussusception. The terminal portion of the ileum, the cecum and the remainder of the right half of the colon were excised and the continuity of the intestine was re-established by side-to-side anastomosis. The pathologist reported that the tumor was a submucous lipoma of the cecum. It was about 5 centimeters in diameter and the overlying mucosa was ulcerated. Situated near the tumor were several pseudopolyps which varied in size from 5 millimeters to 1 centimeter in diameter. The patient's convalescence was uneventful.

CASE 10. A married woman, aged 41 years, came to the clinic on June 6, 1943. She had undergone appendectomy in 1918. In October, 1942, she first had noticed burning pain in the epigastrium 1 hour after meals. It had been relieved by vomiting and by the taking of bicarbonate of soda. Although roentgenologic examination had not disclosed any evidence of peptic ulcer, an ulcer regimen had been instituted. In November, 1942, the patient had had an attack of diarrhea which had lasted 1 month and during which time she had passed from 8 to 10 bloody stools during the day and from 3 to 4 during the night. A similar attack had occurred in February, 1943, but had disappeared in about 3 weeks, although the diarrhea had recurred about 2 weeks later and had persisted until the patient came to the clinic. Cramps in the lower part of the abdomen had accompanied each bowel movement. When diarrhea had not been present, the patient's bowels had moved only with the aid of a cathartic and the stools had been the size of a pencil.

On examination the abdomen was slightly distended and the left lower quadrant was tender. Palpation also disclosed a small mass in this quadrant. Proctoscopic examination disclosed hemorrhoids and a small rectal polyp; the polyp was fulgurated. Roentgenograms of the stomach and gall bladder showed normal conditions. Roentgenologic examination of the transverse colon disclosed a large polypoid tumor in this portion of the colon, situated near the hepatic flexure. The roentgenologist expressed the opinion that there might possibly be several other smaller polypoid tumors, both proximal and distal to the large tumor. The smaller polyps could not be demonstrated satisfactorily by roentgenoscopy because of the presence of intussusception which could not be reduced during the examination.

On June 11, 1943, excision of the terminal portion of the ileum, the cecum and the right half of the colon was performed. The continuity of the intestine was re-established by side-to-side anastomosis. The pathologist reported that the tumor was a pedunculated submucous lipoma which measured 8 centimeters in diameter. An ulcer, 5 centimeters in diameter, was present on the surface of the tumor. The patient was in good health when she was dismissed on June 30, 1946.

CASE 11. A man, aged 53 years, registered on June 19, 1943, because of diarrhea of 2 weeks' duration and of red blood in the stools 7 days before admission. His appendix had been removed in 1917. During the year before he came to the clinic he had been receiving prostatic massage for aching pain in both groins. The massage was continued although the pain had subsided in the past 6 months. Since December, 1942, he had had frequent attacks of mild abdominal cramps which always had been relieved by a bowel movement, the stools having been formed and no blood having been noted. Diarrhea, with 4 to 6 bowel movements daily, had developed 2 weeks prior to admission and medical treatment for the condition had been followed by obstipation. Seven days before registration there had been marked rectal bleeding which had persisted for 36 hours. Two days later, roentgenologic examination had disclosed a lesion of the sigmoid. Three days before he came under our care, severe abdominal cramps developed which were relieved by the onset again of diarrhea.

On physical examination, deep tenderness was noted in the left groin. Proctoscopic examination of the distal 24 centimeters of the intestine revealed that the upper limit of this portion of the intestine was moderately fixed to surrounding structures and that it was angulated anteriorly. Internal hemorrhoids, grade 1+ were present. Roentgenologic examination disclosed a polypoid tumor at the junction of the descending colon and the sigmoid flexure which had a tendency to cause intussusception. The retrograde flow of barium was partially obstructed.

Laparotomy was performed on June 26, 1943, at which time the polypoid tumor was found in the upper part of the sigmoid flexure. Because it was felt that the tumor might be malignant, about 10 inches (25.4 cm.) of the sigmoid flexure was excised. The continuity of the intestine was re-established by end-to-end anastomosis over a three-bladed clamp. The pathologist reported that the tumor was a pedunculated submucous lipoma of the sigmoid flexure, 4 centimeters in diameter. An ulcer, 2 centimeters in diameter, was found on the surface of the tumor. Ten days after the operation, the patient passed a small renal calculus.

On September 16, 1944, the patient returned to the clinic for re-examination. At that time roentgenologic examination of the colon and terminal portion of the ileum did not disclose any abnormality.

CASE 12. A married woman, aged 61 years, came to the clinic on September 22, 1943, because of a painful swelling of the right knee. She was troubled with constipation but she occasionally passed 2 or 3 loose stools daily. She also complained of gaseous distention of the stomach and of belching. Physical examination disclosed tenderness over the cecum and a questionable mass in this region. Roentgenologic examination revealed a polypoid tumor in the right portion of the colon.

Exploratory laparotomy was performed on October 5, 1943. A tumor was found in the ascending colon just above the cecum. The tumor which was situated between the muscular and mucosal layers of the colon was removed by dissection. The pathologist reported that the tumor was a submucous lipoma. It measured 8 by 5 by 2 centimeters. The patient made an uneventful recovery and was dismissed from our care on October 29, 1943.

The patient returned in January, 1946, because of intermittent aching and swelling in the right side of the abdomen. Physical examination did not disclose any abnormality and roentgenograms of the stomach and colon showed normal findings.

CASE 13. A married woman, aged 58 years, came to the clinic on October 26, 1944, because of constipation which had been present for 4 years and which had increased in severity. She said that the constipation could be relieved with enemas. On several occasions the bowel movements had been preceded by the passage of a small amount of mucus and 5 months before admission a small amount of blood had been passed in the stool.

Physical examination revealed an adenoma of the right lobe of the thyroid gland and a palpable mass in the left side of the epigastrium. Roentgenologic examination disclosed a polypoid tumor in the midportion of the descending colon which had caused intussusception.

On November 8, 1944, the involved portion of the descending colon was excised and the continuity of the intestine was re-established by end-to-end anastomosis. The pathologist reported that the tumor was a submucous lipoma which measured 5 centimeters in diameter. An ulcer, 4 centimeters in diameter, was present on the mucosal surface of the tumor.

CASE 14. A married woman, aged 50 years, registered on November 2, 1944. Six weeks previously she had felt a tumor in the middle of the abdomen. Roentgenologic examination of the kidneys and gall bladder had failed to disclose any abnormality. The tumor had disappeared after castor oil had been administered in the preparation of the patient for roentgenologic examination of the colon. She subsequently had felt the tumor on 3 or 4 occasions but it had disappeared after she had taken an enema or a dose of castor oil. She had indigestion and said that she was passing an increased amount of flatus. She always had been constipated.

Physical examination revealed a lipoma, the size of an egg, on the posterior wall of the thorax. Roentgenologic examination of the colon disclosed a polypoid tumor about 5 centimeters in diameter. The tumor appeared to be situated in the descending colon and at times had caused the ascending colon to become invaginated into the transverse colon. Proctoscopic examination did not reveal any abnormality.

On November 14, 1944, excision of the cecum and several centimeters of the ileum was performed and the continuity of the intestine was re-established by side-to-side anastomosis. The pathologist reported

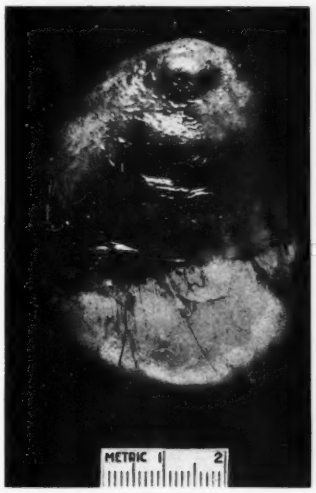


Fig. 1. Case 16. Pedunculated submucous lipoma.

that the tumor was a pedunculated submucous lipoma, 4 centimeters in diameter, which was situated at the juncture of the cecum and the ascending colon. An inflamed ulcer, 1 by 1 by 5 centimeters, was present on the surface of the tumor.

The patient was in good health when she returned to the clinic for examination on October 12, 1945.

CASE 15. A man, aged 62 years, registered on September 18, 1946. Tonsillectomy had been performed in 1928 and a rectal fistula had been excised in 1932. Constipation had been present intermittently for a year and had been associated with pain in the left lower quadrant of the abdomen and with the passage of bright red blood in the stools. However, for one period of 3 months he had not passed any blood. He had not had any diarrhea or obstipation, nor had he lost any weight.

Physical examination did not reveal any abnormality. Proctoscopic examination disclosed hemorrhoids, grade 1. Roentgenologic examination disclosed a large polypoid tumor in the descending colon, just above the level of the crest of the ilium. Since the tumor was radiolucent, the roentgenologist expressed the opinion that it might be a lipoma.

Laparotomy was performed on October 18, 1946. A tumor was found in the wall of the descending colon, just above the level of the anterior superior spine of the ilium. By means of an incision in the serous and muscular coats of the colon, it was possible to remove the tumor without opening the lumen of the intestine. The pathologist reported that the tumor was a submucous lipoma of the descending colon which measured 5 by 3 by 2 centimeters. The postoperative convalescence was uneventful.

CASE 16. A man, aged 55 years, came to the clinic on June 27, 1944, because of hemorrhoids. Proc-

Fig. 2. Case 19. Lipoma with ulceration of overlying mucous membrane.

toscopic examination revealed, in addition to the hemorrhoids, 3 small polyps in the lower 10 centimeters of the rectum. These tumors were fulgurated. Roentgenologic examination disclosed a sessile polypoid tumor in the ascending colon, about 2.5 centimeters in diameter. Removal of the tumor was advised but the patient returned to his home.

He returned to the clinic on October 7, 1946, and at that time he did not have any symptoms that were referable to the gastrointestinal tract. Examination of the abdomen did not reveal any abnormality. Proctoscopic examination disclosed tiny polyps in the last 3 centimeters of the rectum. These tumors were fulgurated. Roentgenologic examination again revealed the polypoid tumor in the ascending colon which appeared at that time to be slightly larger than it had at the time of the patient's previous examination here.

Laparotomy was performed on November 21, 1946. The patient was rather obese and because of the presence of a large amount of fat and many epiploic tags, it was not possible to determine whether or not a polyp was present in the colon. A transverse incision was made in the hepatic flexure and two Deaver retractors were inserted. A yellow polypoid tumor then popped out of the incision. It was freely movable beneath the mucous membrane. It was squeezed from its attachment, the stalk was transfixed and ligated with a double cotton suture and the tumor was excised. The pathologist reported it to be a pedunculated submucous lipoma which measured 4 by 5 by 2 centimeters and weighed 23 grams (Fig. 1).

In a letter dated December 28, 1946, the patient stated that he was in good health.

Case 17. A married woman, aged 49 years, came to the clinic in January, 1947, complaining of spells of extreme weariness and heaviness which were thought to be functional and on a menopausal basis. She complained of gas at the time of these attacks but did not have nausea or vomiting. Some blood had been noted occasionally in the stools.

On examination the patient was found to have moderate hypertension; the blood pressure ranged between 150 and 170 millimeters of mercury systolic and more than 90 diastolic. On proctoscopic examination a small polyp was found 18 centimeters from the dentate margin and this was fulgurated. Roentgenographic examinations of the stomach and gall bladder revealed nothing significant but a spot-film roentgenogram of the colon revealed a sessile, polypoid lesion about 2 centimeters in diameter, in the cecum, just below the ileocecal valve. The growth was not visible in the ordinary roentgenogram.

At operation in February, 1947, appendectomy and transcolonic removal of a lipoma, 2.5 centimeters in diameter, of the cecum were performed. No other abnormality was found except some fibroids of the uterus.

The convalescence was without incident and the patient was dismissed from our care on the twelfth postoperative day.

Case 18. A woman, aged 66 years, came to the clinic in March, 1947, complaining of "gnawing epigastric distress" which had been present for a period of 8 to 10 years. Her gall bladder and appendix had been removed in 1928. She had had chronic constipation for which she habitually had used cathartics and enemas; there had not been any blood in the stools. She had not had nausea or vomiting. Her weight and general physical appearance were normal and physical examination gave essentially negative results except for mild tenderness over the upper part of the abdomen. Roentgenographic examination revealed a large diverticulum of the duodenum and some diverticulosis of the colon but did not disclose any other abnormality in the colon or terminal portion of the ileum.

Surgical treatment was advised for the duodenal diverticulum and, accordingly, on March 17, 1947, resection was performed for the duodenal diverticulum. Further exploration of the abdomen revealed what appeared to be enteritis of the terminal portion of the ileum and a palpable mass in the cecum. Right hemicolectomy was performed with removal of the distal 2½ feet (76.2 cm.) of ileum, the cecum, ascending colon, and hepatic flexure. An end-to-end ileotransverse colostomy was done.

Examination of the removed tissue disclosed multiple nonspecific inflammatory ulcers, in various stages of healing, in the terminal 25 centimeters of the ileum; peri-ileitis had caused angulation of the ileum above the ileocecal valve and had produced mechanical obstruction. Diverticulosis was found in the colon and a submucous lipoma, 1.5 centimeters in diameter was present in the ileocecal valve.

Intermittent episodes of the intussusception might be an explanation of some of the patient's symptoms.

Case 19. A married woman, aged 52 years, came to the clinic in December, 1947, complaining of discomfort in the left lower quadrant of the abdomen of more than 2 years' duration. She had been very ill 2 weeks before admission with intermittent cramps

in the left lower abdominal quadrant, nausea, and vomiting. Bright red blood had been passed in the stool. A mass had been discovered and she had had signs and symptoms of obstruction. She had been hospitalized and a presumptive diagnosis of carcinoma of the colon had been made. Under care, the attacks had lessened in severity and she decided to come to the Mayo Clinic for treatment. The patient stated that she had lost 20 pounds (9.1 kgm.) in the past year and that she was having a constant, dull ache with intermittent crampy pains. A smooth, tender mass was found in the left side of the abdomen. On rectal examination, red blood was noted but there was no mass. Proctoscopic examination for a distance of 26 centimeters also yielded normal findings. A roentgenographic examination revealed an obstructing lesion in the upper portion of the descending colon; it was not possible to force the barium above the lesion, the exact nature of which was indeterminate. Obstruction of the bowel above this level was apparent; there was a large amount of feces in the ascending colon and transverse colon and a loop of small intestine was distended with gas. The lesion did not appear to have undergone malignant change.

Operation was performed on December 20, 1947, at which time an intussuscepting lesion was found in the descending colon. The intussusception was reduced and an incision was made in the colon near the base of the palpable polypoid growth. A lipoma which measured 7.5 by 5.5 by 5 centimeters, with ulceration of the overlying mucous membrane (Figs. 2 and 3), was removed and the colonic incision was closed.

The patient's convalescence was uneventful and she was dismissed from the hospital on the tenth postoperative day.

COMMENT

In the 19 cases which we have reported, the lipomas were distributed rather evenly in the different segments of the large intestine. The site of involvement was as follows: cecum in 6 cases, ascending colon in 4 cases, hepatic flexure in 1 case, transverse colon in 1 case, descending colon in 5 cases, and the sigmoid flexure in 2 cases.

The differential diagnosis of lipoma of the large intestine and carcinoma of the large intestine is rather difficult. In the 19 cases reported herein, the youngest patient was 41 years old and the oldest patient was 66 years old. The average age of the 19 patients was 52 years, which closely approximates the age at which carcinoma of the colon is most likely to occur. Twelve of the 19 patients were women and 7 were men.

Although the symptoms of submucous lipoma closely resemble those of carcinoma, certain rather subtle differences become evident when a group of cases of submucous lipoma are compared with a group of cases of carcinoma. It should be emphasized, however, that these differences are of doubtful value in trying to distinguish these two lesions in an individual case. The symptoms of submucous lipoma may be of much longer duration than those of carcinoma. In the 19 cases which we have reported, the longest duration of symptoms was 15 years and the shortest was 2 weeks. One patient did not have any symptoms that were referable to the gastrointestinal tract. Bleeding may or may not be a sign of lipoma of the colon. In 9 of these 19 cases, blood in the stools had been noted. Anemia was by no means a prominent finding, certainly not comparable to the extent that it is found in the presence of malignant lesions.

Fig. 3. Case 19. Same as Figure 2. Lipoma opened.

Pain, usually intermittent and often of cramping type, was present in 12 of the 19 cases, most probably the result of intussusception. Intussusception tends to occur when the lipoma exists in a mobile portion of the colon and for this reason intussusception occurs more commonly, although not exclusively, when the lipomas are located in the right portion of the large bowel.

If one considers the cecum, ascending colon, hepatic flexure and the first portion of the transverse colon as the right portion of the colon, in 12 of the 19 cases, the lipoma was situated in this segment and in 8 of these 12 cases a one stage resection was performed. In

only 4 of the 12 were the lipomas removed transcolonically.

In 3 of the 7 cases in which the lipoma was situated in the left portion of the colon, segmental resection was required; in the remaining 4 cases local excision of the lipoma was performed.

A total of 11 cases out of 19 in which extensive resection for lipoma was required, might appear on the surface to be a high incidence. However, the difficulties encountered in making an unequivocal preoperative diagnosis, despite the improvement in roentgenologic studies, and the extensiveness of the process of intussusception so often encountered at the time of operation play a part in influencing the surgeon to employ a more radical operation than otherwise might be indicated for a benign condition. It is interesting and significant also that, despite such major surgical procedures, no deaths occurred.

REFERENCES

1. Bauer, J. G. Quoted by Stetten, D. Surg. Gyn. Obst., 1909, 9: 156-176.
2. Comfort, M. W. Surg. Gyn. Obst., 1931, 52: 101-118.
3. Pack, G. T., and Booher, R. J. Surg. Clin. N. America, 1947, 27: 361-372.
4. Pemberton, J. deJ., and McCormack, C. J. Am. J. Surg., 1937, 37: 205-218.

CARCINOID TUMORS OF THE INTESTINE

ORVILLE F. GRIMES, M.D., and H. GLENN BELL, M.D., F.A.C.S., San Francisco, California

ARGENTAFFIN tumors of the intestinal tract are a challenge to modern surgery because of their rarity, their altered behavior in different anatomical locations, and because in only an occasional instance has a correct diagnosis been made preoperatively. The early writers stressed the association of these tumors with "obliterative appendicitis" and noted that they did not infiltrate extensively and only rarely metastasized to regional lymph glands. In spite of these observations no suspicion was aroused that these were not ordinary adenocarcinomas. In 1888, Lubarsch reported 2 cases wherein multiple small separate tumors were noted in the submucosa of the terminal ileum. These consisted of columns and masses of cells which were distinctly unlike those of ordinary carcinoma. No true glandular formation was present, although degeneration of some of the central cells sometimes produced a pseudoglandular appearance. Although he was well aware that these were not the usual type of carcinoma, the cases were reported as primary carcinoma of the ileum.

Oberndorfer, in 1907, clarified the polemic aspects of the problem by showing that there occurred in the gastrointestinal tract, in addition to the ordinary carcinomas, a superficially related tumor for which he coined the term "carcinoid." The important features of the latter were their localized nature and relative benignity as shown by their slow growth and lack of infiltration, the absence of metastatic spread by lymph and vascular channels, the fact that more than one tumor was often present, and their histological appearance. Oberndorfer's ideas were generally accepted, but even as late as 1921 histologically similar tumors were being reported as spheroid-cell carcinoma (23).

In 1914 Gosset and Masson showed that the cells of the intestinal chromaffin tissue when stained by ammoniacal silver salts exhibited black granules in their cytoplasm. By this method they were able to demonstrate similar cells lying among the ordinary columnar cells near the bases of the crypts of Lieberkuehn. Using similar stains they showed that carcinoid tumors were composed of cells of the same type. They therefore added the term "argentaffin" to these tumors. Although Masson's work is not accepted completely, there is almost general agreement that carcinoid tumors originate from the Kultschitzky cells of the crypts of Lieberkuehn. They probably should be called argentaffinomas, but the term carcinoid is so deeply entrenched in medical literature that its continued use seems justifiable.

The Kultschitzky cells are more common in the appendix than elsewhere in the intestine, which accounts for the high incidence of carcinoid tumors in that organ. Their incidence

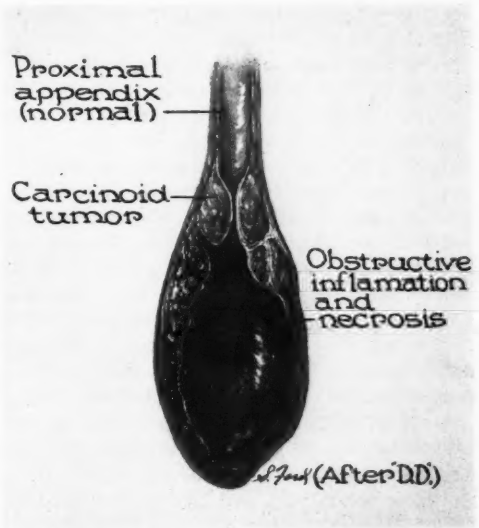


Fig. 1. The characteristic yellow submucosal tumor may obliterate the lumen and cause obstructive inflammation and necrosis of the distal appendix. The irregular lobulation caused by the fibrous tissue septa is evident. The overlying mucosa is usually intact.

From the Department of Surgery, University of California Medical School, San Francisco.

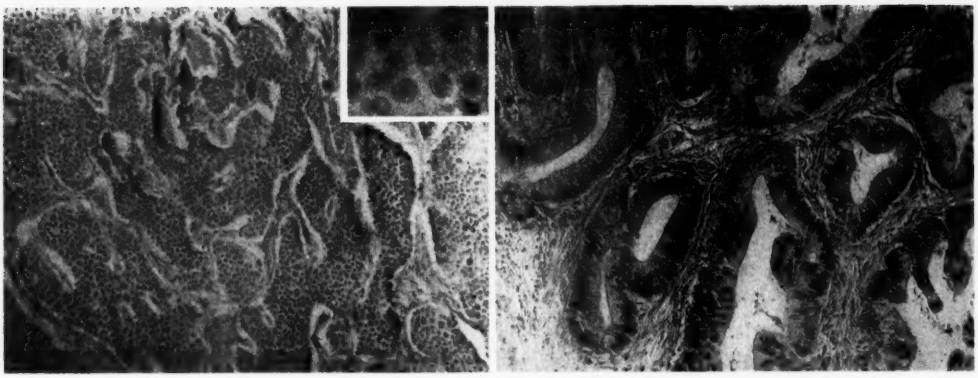


Fig. 2. The columns and masses of cells of the carcinoid tumor, a, left, are distinctly unlike those of the more common adenocarcinoma, b. There is no true glandular formation. The cells are of quite uniform size and are surrounded by a rather dense fibrous tissue stroma which tends to be condensed at the borders of the tumor. The cells have round, distinct nuclei but the cellular borders are often ill defined, a, insert.

is next highest in the terminal ileum, as is the incidence of carcinoids. The neoplasm grows but slowly and is often unrecognized because of its small size. In a small, blind tube like the appendix it is more readily discovered than in the ileum. Of greater importance, however, is the possibility of appendiceal obstruction and the consequent inflammation by which attention may be drawn to it.

In spite of the rather extensive literature concerning them, such tumors are rare. Although 90 per cent of all neoplasms found in the appendix are carcinoids, Foot states that only 0.46 per cent of appendices removed for appendicitis contain carcinoid tumors. A single tumor is usually present, most frequently in the tip; in most of the reported series, from 70 to 80 per cent occurred in this region. Elsewhere in the gastrointestinal tract multiple tumors are more commonly encountered. After the appendix, the terminal ileum is the next most common location, though they may occur anywhere in the gastrointestinal tract from the cardia to the rectum and constitute about 20 per cent of all malignant tumors arising in the small intestine.

Characteristically the tumor consists of a yellow nodule of varying size which occupies the submucosa. The overlying mucous membrane is usually intact although occasionally some superficial ulceration occurs. The nodule has a firm, rubbery consistency and may extend through the muscularis to involve the serosa. The cut surface of the tumor often exhibits irregular fibrous bands dividing it into more or less separate yellow nodules. In the appendix, as it increases in size the tumor may reach the opposite wall and cause obstruction of the lumen (Fig. 1). In other instances it appears as an annular thickening of the appendiceal wall, frequently a centimeter or more in length, which completely obliterates the lumen. In either event an attack of acute obstructive appendicitis may occur. It should be noted that the tumor obliterates the lumen not by contraction of the fibrous stroma but by its bulk. At the opposite extreme, the lesion may be so small that it is found only on microscopic examination. Elsewhere in the gastrointestinal tract, where the lesions are more often multiple, the growths usually project into the bowel lumen as smooth polypoid masses over which the mucosa is intact. A rather intense fibroplasia accompanies the invasion of the mesentery resulting in kinking of the bowel by contraction of the fibrous tissue. Occasionally the tumor assumes a ring-like constriction similar to that of adenocarcinoma.

Microscopically the tumor consists of clumps and masses of large spheroidal cells lying in a fibrous stroma. There is usually some condensation of the nonstriped muscle fibers at the periphery of the tumor in the fibrous capsule which tends to form. The

TABLE I.—CLINICAL RÉSUMÉ OF CARCINOID TUMORS OF THE APPENDIX SEEN AT THE UNIVERSITY OF CALIFORNIA HOSPITAL, 1927–1947

Case	Age	Sex	Involvement			Acute inflammation	Submucosal fibrosis	Normal appendix
			Muscularis	Serosa	Mesoappendix			
1	28	M		×		×		
2	60	M		×				×
3	65	M		×			×	
4	38	F	×				×	
5	21	F	×				×	
6	15	F	×					×
7	22	F			×			×
8	31	F	×			×		
9	13	F	×					×
10	13	F		×		×		
11	18	F		×		×		
	Average age: 29.5	3 males 8 females	5 cases = 45.5%	5 cases = 45.5%	1 case = 9%	4 cases = 36.4%	3 cases = 27.2%	4 cases = 36.4%

Table I. Appendiceal carcinoids are most often seen in young females. Growth by continuity involves successively the muscularis, the serosa, and occasionally the mesoappendix. The tumors are encountered about equally in the normal and in the acutely or chronically diseased appendix.

cells often extend beyond this, however, and cell nests may be seen in the muscularis, the subserosa, the serosa or even in the adjacent peritoneum or mesentery (4).

The cells have round, distinct nuclei but often the cytoplasmic borders are ill defined. They bear no resemblance to the ordinary columnar or mucous cells lining the intestinal glands. There is no true glandular formation. Occasionally the central portions of the cell masses exhibit a vacuole which contains an eosin-staining material. This formation may closely simulate the rosettes which occur in the neuroblastomas (Fig. 2).

Although the characteristic feature of the tumor as originally described was its apparent benignity, it is now generally agreed that malignant change may occur. Spread occurs by continuity and contiguity of tissue as well as by invasion of lymph and vascular channels. In the small intestine such a change is rather commonly encountered. Appendiceal carcinoids, however, are but rarely malignant.

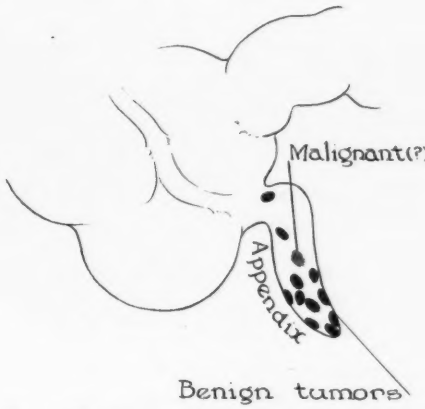


Fig. 3. Nine (82 per cent) of the 11 appendiceal carcinoids were located in the distal portion of the appendix and only 2 in the proximal extent. Widespread abdominal involvement in 1 case may have been due to a carcinoid tumor originating in the appendix.

In 1926, Stewart and Taylor reported 1 case and could find only 8 others cited in the literature. Wyatt recently has been able to collect another 5 cases.

It is becoming apparent that the behavior of the carcinoid tumors is quite different depending upon the site of the primary growth. Those arising in areas other than the appendix may appear as metastasizing malignant growths requiring radical treatment.

In the 21 year period from 1927 through 1947, 19 patients were treated at the University of California Hospital for carcinoid tumors of the gastrointestinal tract. Eleven were in the appendix and 8 in the small bowel. The behavior of the tumor in each group is so different that it seems best to discuss them separately.

CARCINOID TUMORS OF APPENDICEAL ORIGIN

Appendiceal carcinoids occur usually in young people and are more commonly seen in females. The oldest patient in the University of California group was 65, the youngest 13, and the average age was 29.5 years. All were treated by simple appendectomy. One tumor was located in the proximal end, 1 in the mid-portion, and the remaining 9 (82 per cent) were in the tip of the appendix (Fig. 3). Five of the carcinoids involved the muscularis

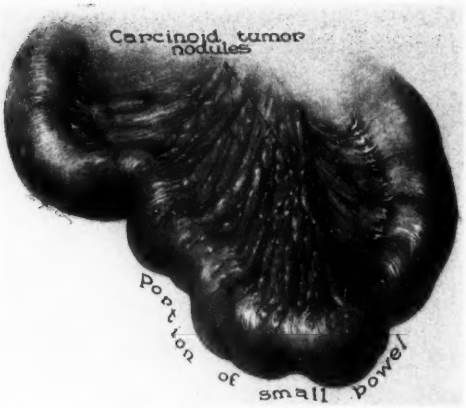


Fig. 4. An intense fibroplasia accompanies the invasion of the mesentery by the carcinoid tumor. The resultant mesenteric contraction may produce kinking of the intestine to cause obstruction. In the roentgenographic examination, the kinking of the bowel in association with an intraluminal tumor suggests the diagnosis.

only, 5 involved the serosa as well as the muscularis, and 1 extended into the adjacent mesoappendix. The mucosa overlying each was intact. Four of the appendices showed acute inflammation, 3 showed submucosal fibrosis, and 4 were not abnormal. The tumors all had histologically similar characteristics even though one showed invasion of the mesoappendix. Follow-up is admittedly inadequate, but there have been no reported sequelae from any of the group of patients (Table I).

Hence, appendiceal carcinoids seen at the University of California Hospital conform to the generally accepted clinical and histological characteristics indicated in other reports in the literature. Patients whose appendices contain these tumors usually have no sequelae when the appendix is removed. Cell nests are seen about equally as frequently in the muscularis as in the serosa and, if growth by continuity into the mesentery can be considered a criterion of malignancy, then an occasional one is malignant. They are found about equally in the normal and in the acutely or chronically diseased appendix. It is probable that because of the location in a narrow, blind-ending tube, carcinoids of the appendix produce symptoms relatively early and are therefore removed at an earlier stage than are similar tumors located elsewhere in the gastrointestinal tract. It may well be that in the appendix, as elsewhere, metastases and therefore malignancy are merely a matter of time. Since attention is called to the appendix early, carcinoid tumors may be removed while they are still localized to that organ and for that reason the benignity of appendiceal carcinoids may be more apparent than real. Certainly the growth and histologic characteristics of the tumor in any location are identical.

CARCINOID TUMORS OF EXTRA-APPENDICEAL ORIGIN

Argentaffin tumors arising elsewhere in the gastrointestinal tract present quite different problems. In this instance the tumor is likely to assume definitely malignant characteristics manifested by metastases, most of which are either to the regional lymph nodes or to the adjacent peritoneum or mesentery.

In the small intestine carcinoid tumors occur mostly in older people, and the multiplicity of primary lesions is in contrast to the single primary nodule occurring in the appendix in younger age groups. In those patients in our series having carcinoid tumors of the small intestine, the oldest was 67, the youngest 41, and the average age was 58 years (Table II). These observations agree with those of Cooke who, in a summary of the literature, noted an average age of 57.2 years in patients having malignant carcinoid tumors of the small intestine. These figures contrast markedly with the average age of 29.5 years for patients in whom appendiceal carcinoids were found. Appendiceal carcinoids were more often seen in females while small bowel carcinoids occurred in 5 men and 3 women in this group. This proportion is maintained throughout the literature.

The most common clinically observed syndrome was recurrent attacks of partial intestinal obstruction associated with pain, diarrhea, and weight loss. Five of the 8 patients with small bowel argentaffin tumors manifested this tetrad of symptoms and signs. This proportion is high in comparison with other accounts appearing in the literature. Cooke, collecting informative data from the world literature, noted that about 50 per cent

TABLE II.—CLINICAL RÉSUMÉ OF MALIGNANT CARCINOIDS SEEN AT THE UNIVERSITY OF CALIFORNIA HOSPITAL 1927 THROUGH 1947

Case Age Sex	Symptoms and signs	Primary lesion	Metastatic deposits	Operative treatment	Postoperative treatment	Sequelae
1 55 F	Abdominal pain, diarrhea, wt. loss of 50 pounds, and partial small bowel obstruction	Upper portion of ileum	Mesenteric and periaortic nodes	Biopsy and entero-enterostomy	Large bowel obstruction requiring transverse colostomy 2 yrs. later	Died 44 mos. after enteroenterostomy with generalized abdominal metastases
2 55 M	Diarrhea, weight loss, right lower quadrant mass	Undetermined; possibly appendiceal	Omentum, peritoneum, large and small bowel, retroperitoneal tissues, pelvis	Biopsy	None	Died (10 months postoperative). Generalized abdominal metastases
3 60 M	Lower abdominal pain	Terminal ileum	Adjacent mesenteric nodes	Ileocolic resection (with wide margin of mesentery)	None	No recurrence; 7 years (proved at second laparotomy for marginal ulcer)
4 41 M	Dyspnea, anemia, blood in stool, mass in left flank	Probably primary in jejunum	Generalized abdominal spread, including liver and spleen	Biopsy	Radiation	Died 23 mos. postoperative with generalized abdominal metastases
5 61 M	Epigastric distress, cramps, vomiting, wt. loss of 15 pounds. Small bowel obstruction	Terminal ileum	Adjacent mesentery by continuity	Ileotransverse colostomy (tumor not removed)	Biopsy of recurrence in abdominal wall scar	Died 50 mos. postoperative with generalized abdominal metastases
6 64 F	Diarrhea, cramps, small bowel distention. Weight loss	Undetermined; probably terminal ileum	Mesenteric nodes, periaortic nodes, liver	Biopsy	None	Died: 10 days postoperative.
7 60 F	Generalized abdominal pain, diarrhea, and symptoms of small bowel obstruction	Terminal ileum	Cul-de-sac extending into vagina	Resection, and lateral anastomosis	1. Biopsy pelvic mass 2. Irradiation	Died: 10 years after original surgery
8 67 M	Diarrhea, intermittent abdominal pain, distention, partial large bowel obstruction	Terminal ileum	Omentum, small bowel, mesentery, peritoneum, internal mammary node	Laparotomy and biopsy	None	Died: 8 months after laparotomy

Table II. The average age was 58 years in the 5 males and 3 females in the series. All the tumors were malignant as shown by regional and distant lymphatic and blood borne metastases. Carcinoid tumors should no longer be regarded as clinically silent neoplasms. Operative results are exceptionally good when it is possible to excise the tumor with a wide margin of gland bearing mesentery. Even in the presence of distant metastases a tendency toward stabilization of the metastatic deposits is noted when the primary growth is removed.

of malignant carcinoid tumors produced clinical symptoms, although the majority of authors indicate a much lower percentage. It is becoming apparent that no longer should these neoplasms be regarded as clinically silent lesions. As one would suspect from the rather intense fibroplasia accompanying the mesenteric invasion, obstruction results either from the kinking of the bowel by contraction of the mesentery or from intussusception occasioned by the partially intraluminal mass or masses.

Diarrhea was not only common but often severe. It is only rarely that blood can be demonstrated in the stool, since the lesions usually do not cause ulceration of the mucosa. Abdominal masses were palpable in 2 patients. Their presence indicates metastatic spread since the primary lesions are almost always small (Table III).

It was true in this series, as in other accounts reported in the literature, that in spite of the suggestive clinical syndrome, the nature of the disease was not suspected before operation. Indeed, in some cases, the possibility of the existence of a tumor of such nature was not entertained even at surgery. A perusal of the literature reveals that a correct diagnosis of carcinoid tumor of the bowel is made but rarely before operation. In 1942 Miller and Herrmann published the case history of a patient in whom a correct diagnosis was obtained prior to laparotomy. They indicated that in the presence of dilatation of the small bowel from carcinoid tumors a small filling defect associated with kinking of the bowel in that segment could be demonstrated roentgenologically. Coexistence of kinking and tumor of the bowel suggests the diagnosis (Fig. 4).

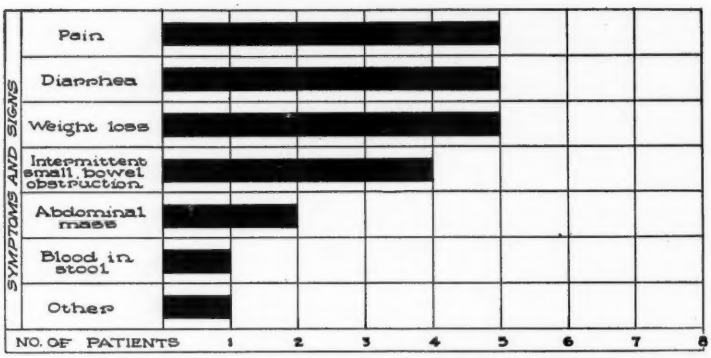


Table III. Pain, diarrhea, and weight loss in association with intermittent episodes of small intestinal obstruction formed the most commonly observed clinical syndrome. The presence of a carcinoid tumor of the small bowel should be suspected when this tetrad of symptoms and signs is encountered. Blood is found but rarely in the stool, for these tumors usually do not cause ulceration of the mucosa. The presence of palpable abdominal masses usually indicates widespread inoperable abdominal involvement.

The lesions were primary in the ileum in 5 of the 8 patients. In 1 patient, although the primary site could not be ascertained with exactitude, it was strongly suspected to have been primary in the terminal ileum also. The jejunum was the primary site in 1 patient. In the remaining case, because of the widespread deposits within the abdomen it was utterly impossible to determine the site of origin. Since the distal one-third of the appendix was involved it was the opinion of the operator that the tumor could have arisen from the appendix. Our observations agree with most published reports which indicate that the terminal ileum is the most common site of origin of carcinoid tumors of the small bowel (Fig. 5).

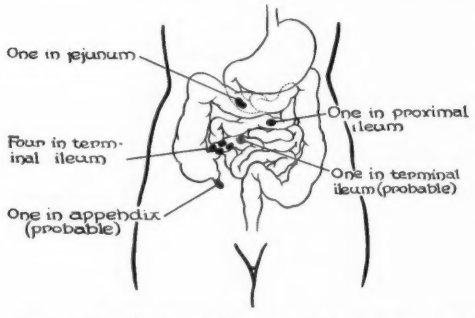


Fig. 5. Five (and probably one other) of the carcinoid tumors originated in the terminal ileum. The Kultschitzky cells from which these tumors arise are common in the terminal ileum which accounts for the high incidence in this location.

Metastases, present in all patients, occurred most often in the regional lymph nodes, the mesentery, and the adjacent peritoneum. Distant metastases were much less frequent, although metastases in the liver and spleen and even within the thorax were noted in this series (Fig. 6). Once the tumor reaches the peritoneal surface of the bowel, it may implant itself elsewhere just as do other malignant tumors. Ariel, in 1939, summarized the literature and noted that of the 237 small intestinal carcinoid tumors reported to that date, only 24.9 per cent showed evidence of metastases. Dockerty and Ashburn studied 30 carcinoid tumors of the small bowel in which 13 showed undoubted evidence of metastases. This represents a percentage of 43.3 which were malignant. Humphreys in 1934 reviewed 152 cases and found 37 (24.4 per cent) that had metastases. Dangremond, reviewing 42 cases in 1942, found metastases in 24 (52 per cent).

The problem of metastases is an important one for it was only 20 years ago that Forbus emphasized the benign nature of carcinoid tumors. In recent years, however, their malignant tendencies have been recognized although certainly not universally. Our group,

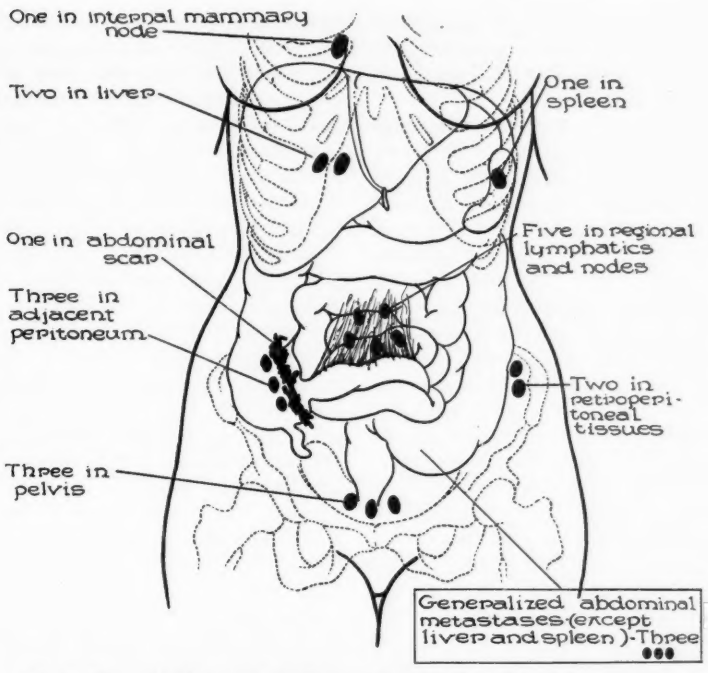

One in internal mammary node
Two in liver
One in spleen
One in abdominal scar
Five in regional lymphatics and nodes
Three in adjacent peritoneum
Two in retroperitoneal tissues
Three in pelvis
Generalized abdominal metastases (except liver and spleen)-Three

Fig. 6. The predominant metastatic spread is regional involving the mesentery, its nodes, and the adjacent peritoneum. Metastatic deposits were encountered in both the liver and spleen. Spread occurs by continuity and contiguity of tissue as well as by invasion of lymph and vascular channels.

all of which manifested the usual criteria of malignancy, again forcefully emphasizes that carcinoid tumors of the small bowel should be considered as malignant lesions.

Because of the malignant tendencies of argentaffin tumors, treatment should be as radical as is possible. It is fortunate that most of the lesions occur in the terminal ileum so that extensive resections are possible. Horsley has advocated resection of carcinoid tumors even in the presence of metastases and other authors concur, for it is not unusual to see metastatic deposits become stationary after the removal of the primary growth. In the 2 cases in our series where wide resection of the tumor and gland-bearing area was possible, 1 patient has an apparent cure 7 years after surgery, as shown by a second laparotomy for treatment of a marginal ulcer; the other lived 10 years before succumbing to large pelvic metastases. Even in those cases in which spread of the tumor made resection impossible, the average survival after diagnosis of inoperability was 27 months (excluding the single mortality in the immediate postoperative period) (Table IV). It is apparent that these tumors do truly represent a challenge to modern surgery, for with the possibility of early diagnosis combined with

TABLE IV.—COMPARATIVE SURVIVAL OF PATIENTS OPERATED UPON

No. of patients	Operative treatment	Average time of survival
2	Wide resection of tumor and mesentery	8.5 years
2	Enteroanastomosis and biopsy	47 months
4	Biopsy only	12 months

Table IV. The excellent prognosis when resection is possible is quite apparent. As indicated in other accounts in the literature, simple sidetracking of the lesion is advantageous. The survival time for the 6 patients in whom resection was not possible averaged 27 months.

their relatively slow growth one would expect carcinoid tumors to be more amenable to surgical treatment than other malignant tumors of the intestine.

Prognosis depends upon the presence or absence of irremovable metastases. However, even in their presence patients may live for many years after their recognition. Stewart and Taylor's patient was alive 10 years after developing metastases, and Mallory's patient lived for 20 years. This relative longevity may be attained even in those cases in which only a shortcircuiting operation is possible. Terplan, Weintraub, and Wolf report the case history of a patient who survived 5 years after ileocolostomy for a carcinoid tumor with hepatic metastases. The patient died by drowning 5½ years after operation. Necropsy examination showed that there was regression of the primary tumor, and the hepatic metastases had remained without further growth.

Few reports have mentioned the use of radiation in the treatment of carcinoid tumors. In Ariel's case (1939) a probable metastasis in the right iliac fossa was treated by radiation with disappearance of the tumor. Bailey has suggested that the postoperative use of radiation may improve still further the relatively good prognosis of this type of intestinal tumor. Two of our patients received radiation therapy given as a palliative measure. It is impossible to draw conclusions concerning the benefits of such therapy from the observation of these patients.

SUMMARY

In addition to the ordinary adenocarcinomas, superficially related tumors known as carcinoid or argentaffin tumors also appear in the gastrointestinal tract. They occur as single nodules in the appendix but are more often multiple elsewhere in the gastrointestinal tract. In the appendix they appear in young people, contrasting markedly with their appearance elsewhere in patients whose average age is 58 years. This report concerns 11 such tumors arising in the appendix and 8 whose origins were in the small intestine. Those appearing in the appendix occurred as submucosal nodules extending peripheralward to involve in succession the muscularis, the serosa, and in 1 instance the mesoappendix. All were treated by simple appendectomy after which no sequelae were noted. At the opposite extreme are the 8 patients exhibiting small bowel argentaffin tumors, all of which manifested malignant characteristics as shown by local or distant metastatic spread. The similarity of histologic pattern and growth tendency leads one to believe that the tumors in either location are similar if not identical and that metastases and therefore apparent malignancy are merely a matter of time. In a small, narrow blind-ending tube such as the appendix attention is called to the organ early so that the tumor is still a localized one when removed by simple appendectomy. In the small bowel such early signs as are present are most often confused with abdominal conditions not requiring immediate surgical intervention. Hence intestinal tumors are not reached at such an early stage as are those in the appendix so that metastases have had time to develop.

Carcinoid tumors of the small bowel are most often seen in the terminal ileum. Their predominant spread is regional, but widespread abdominal or distant metastases may occur just as in the more common adenocarcinomas.

Attention is called to the four most common symptoms and signs noted in carcinoid tumors of the small bowel. The tetrad of intermittent episodes of small bowel obstruction associated with abdominal pain, diarrhea and weight loss is so common, and indeed quite characteristic, that consideration of such tumors is strongly advised when this syndrome appears. The roentgenological study of the small intestine in an attempt to demonstrate both kinking and tumor of the bowel is an important aid in obtaining a correct and early preoperative diagnosis.

The excellent results obtained from wide excision of the tumor bearing area cannot be too strongly emphasized. Even when distant metastases have already occurred, it is not unusual to note a tendency toward stabilization of the metastatic deposits after the primary lesion has been removed. Postoperative radiation may be beneficial for there is suggestive though incomplete evidence that car-

cinoid tumors may be radiosensitive. It is because of these therapeutic tangibles that one should be especially alert to the possibility of the presence of carcinoid tumors. With early diagnosis and adequate resection one can expect better results in the surgical treatment of these tumors than in any other intestinal malignancy.

ADDENDUM.—Since completion of this report, one other patient has been treated for a malignant tumor, probably arising in the cecum. A white man, age 73 years, had minor episodes of generalized abdominal pain associated with diarrhea for about 1 year. Shortly before admission he noted tenderness in the right lower abdomen. He had lost 15 pounds during the year's illness. No palpable masses were noted in the abdomen but a polypoid lesion was encountered in the rectum, biopsy of which demonstrated histologic evidence of malignant tumor. A filling defect in the cecum was shown by a barium enema.

Laparotomy revealed a firm mass in the cecum extending into the ascending colon. There were numerous widely scattered implants onto the peritoneum, omentum, and the mesentery of both the right colon and the ileum. Nodular areas could be palpated in the liver, but these were not visible on its surface. Microscopic examination of one of the implants revealed the familiar pattern of carcinoid tumor.

REFERENCES

1. ARIEL, I. M. Arch. Path., 1939, 27: 25-52.
2. BAILEY, O. T. Arch. Path., 1934, 18: 843-864.
3. BONAR, A. A. Brit. M. J., 1946, 1: 391-392.
4. BOYD, WILLIAM. Surgical Pathology. 5th ed. Philadelphia and London: W. B. Saunders Co., 1942.
5. COOKE, H. H. Arch. Surg., 1931, 22: 568-597.
6. DANGREMOND, G. Am. J. Clin. Path., 1942, 12: 223-231.
7. DICKSON, J. A. Surg. Gyn. Obst., 1946, 82: 675-681.
8. DOCKERTY, M. B., and ASHBURN, F. S. Arch. Surg., 1943, 47: 221-246.
9. FOOT, N. C. Pathology in Surgery. Philadelphia: J. B. Lippincott Co., 1945.
10. FORBUS, W. D. Bull. Johns Hopkins Hosp., 1925, 37: 130-153.
11. GOSSET, A., and MASSON, P. Presse méd., 1914, 22: 237-240.
12. HORSLEY, J. S. J. Am. M. Ass., 1941, 117: 2119-2123.
13. HUMPHREYS, E. M. Am. J. Cancer, 1934, 22: 765-775.
14. LUBARSCH, O. Arch path. anat., 1888, 111: 280-317.
15. MALLORY. In discussion of Cabot case report. N. England J. M., 1940, 222: 684-687.
16. MILLER, E. R., and HERRMANN, W. W. Radiology, 1942, 39: 214-220.
17. MOORE, T. Brit. J. Surg., 1938, 26: 303-313.
18. OBERNDORFER, S. Frankf. Zschr. Path., 1907, 1: 426-432.
19. REYNOLDS, R. P., and CANTOR, M. O. Am. J. Surg., 1946, 71: 705-709.
20. RIGDON, R. H., and FLETCHER, D. E. Am. J. Surg., 1946, 71: 822-824.
21. STEWART, M. J., and TAYLOR, A. L. J. Path. Bact., 1926, 29: 136-139.
22. TERPLAN, K., WEINTRAUB, D., and WOLF, N. J. Arch. Path., 1940, 30: 1155.
23. WILKIE, D. P. D. Brit. J. Surg., 1920–21, 8: 392-396.
24. WYATT, T. E. Ann. Surg., 1938, 107: 260-269.

THE ROLE OF THE PERITONEAL REFLECTION IN THE PROGNOSIS OF CARCINOMA OF THE RECTUM AND SIGMOID COLON

JOHN W. KIRKLIN, M.D., MALCOLM B. DOCKERTY, M.D., and
JOHN M. WAUGH, M.D., F.A.C.S., Rochester, Minnesota

ALTHOUGH studies on the factors affecting the prognosis of carcinoma of the rectum and lower part of the sigmoid colon are not new, the present availability of a number of operative procedures for lesions in this region has stimulated increased thought and attention to these factors. Segmental resection with end-to-end anastomosis (3, 15), modifications of the Hochenegg pull-through procedure (1), and low segmental resection with anastomosis through the sacral or perineal approach (11, 13), all have now appeared to challenge the classical combined abdominoperineal resection for carcinoma in this region. These procedures preserve function of the anal sphincter, to some degree at least, and do not necessitate a permanent abdominal colostomy.

An accurate appraisal of the merits of these procedures and the indications for their employment depends on several considerations. Differences in operative mortality must of course be ascertained. The adequacy of function of the sphincter when these procedures are used and the merits of such function in comparison with a colonic stoma should be known. An understanding of the factors affecting prognosis in cases of carcinoma of the rectum and lower part of the sigmoid colon is of fundamental importance in the selection of a curative operative procedure. Although there are many such factors, we are concerned here with only one of these, namely, the relation of the location of the growth to the level of the reflection of the pelvic peritoneum from the wall of the bowel.

Some surgeons consider that the prognosis when lesions lie below the peritoneal reflection is inherently poorer, other factors being equal, than when lesions lie above this reflection in a portion of bowel covered by serosa. Thus these same surgeons tend to employ a more radical procedure, usually combined abdominoperineal resection, for lesions below the peritoneal reflection although other factors might have permitted a procedure which allowed preservation of the anal sphincter.

It thus seemed of value to determine whether or not the location of the lesion with reference to the peritoneal reflection has any influence on the prognosis in cases of carcinoma low in the sigmoid colon and high in the rectum. A careful review of the literature failed to reveal a single study of this matter. Therefore, the present investigation was undertaken.

Since this project was completed, however, the most recent of the careful studies on carcinoma of the intestine carried out by Gilchrist and David has been published. These authors found that in their cases colonic carcinoma situated partially or completely below the peritoneal reflection had a relatively high incidence of recurrence and metastasis, and thus that in their group the prognosis in such cases was poorer than in cases in which the lesions were completely above the peritoneal reflection. It might seem, from this, that the location of the growth in relation to the peritoneal reflection does have an effect on prognosis.

Close study of the report of Gilchrist and David revealed, however, that their findings with regard to the effect of the location of

Abridgment of thesis submitted by Dr. Kirklin, fellow in Surgery, Mayo Foundation, to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Master of Science in Surgery.

From The Division of Surgical Pathology and The Division of Surgery, Mayo Clinic.

the lesion in respect to the peritoneal reflection were incidental and not the primary concern of their study. They, therefore, did not exercise certain controls which we employed. These are (1) elimination of low-lying lesions which may affect prognosis unfavorably, (2) maintenance of uniformity of histologic grade and type of lesion (Dukes), and (3) comparison of lesions which were essentially at the same level in the bowel, some of which were above and others below the peritoneal reflection.

MATERIAL AND METHODS

The material for this study was selected in such a way that all factors which might influence prognosis were controlled, except the relation of the location of the lesion to the level of the peritoneal reflection.

All cases in which an adenocarcinoma of the rectum, rectosigmoid, and lower part of the sigmoid colon was removed by combined abdominoperineal resection in one or two stages, from 1916 through 1940, were selected from the files of the Mayo Clinic. From this large group, all cases in which the adenocarcinoma had been graded 2 (the Broders method, 2) by the pathologist previously examining the specimen were selected. From this group were eliminated all cases in which a metastatic lesion was demonstrable in the liver at the time of operation, those in which resection for some other reason was considered only palliative and those in which the patient died during the postoperative period of hospitalization.

In this manner, 296 cases were obtained and the formalin-preserved, gross specimen removed in each of these was available for examination. Each of these gross specimens was carefully re-examined, and 137 of them were found to be suitable for inclusion in the present study. The remainder were discarded because of failure to conform to one or more of the following requisites for inclusion in this series: (1) The lesion must have been located completely above the level of the peritoneal reflection, or completely below it. Lesions lying mainly above or below this level, but going over it in part were discarded. (2) The lower edge of the lesion must have been at least 2 centimeters removed from the anal margin, as measured in the fixed specimen. This second requisite was adopted in order to eliminate the extremely low-lying lesions whose mode of spread may differ from that of higher-lying rectal lesions and hence whose curability may differ. (3) The lesion must have been the only carcinoma in the specimen removed; multiple primary carcinomas were thus excluded. Adenomatous polyps were not considered to be carcinomas, and thus their presence did not eliminate a case from inclusion in the study. (4) Enough of the gross specimen must have been present to allow adequate identification of the peritoneal reflection, measurement of the distance from the lower edge of the lesion to the anal margin and selection of tissue for microscopic examination from the lesion and from the regional lymph nodes. Only a few cases were eliminated because the specimen failed to meet this last specification.

Each of the 137 gross specimens finally selected was carefully examined and a sketch was made of each. The size of the carcinoma and its situation with respect to the level of the peritoneal reflection and to the anal margin were noted. Incisions from the serosal surface or from that of the fascia propria to the mucosal surface were made transversely to the long axis of the bowel at intervals of approximately 0.5 centimeter. These thin slices hinged on the uncut mucous membrane and greatly facilitated the search for involved lymph nodes. Each specimen was carefully dissected for such nodes, and any that were suspected of being involved were removed and transferred to bottles containing a fresh 10 per cent solution of formalin. These specimens were subsequently sectioned with the freezing microtome, cut at 10 microns thickness, stained in the routine manner with hematoxylin and eosin, and examined microscopically for the presence of metastatic carcinoma. The primary growth was cut across through its most deeply ulcerated part, and note was made whether it had involved perirectal fat or had penetrated the serosa. Sections were then taken from the deepest extent of the growth, from all regions of apparent subserosal or serosal infiltration,

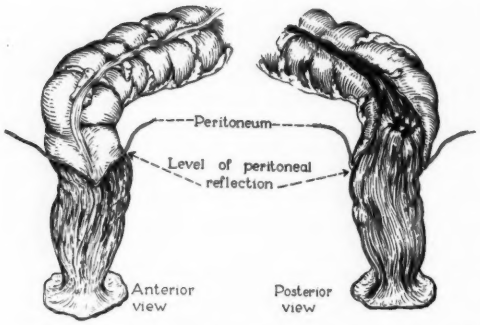


Fig. 1. The peritoneal covering of the rectum and lower part of the sigmoid colon. A growth at the location sketched has relatively little opportunity for direct serosal invasion, even though it lies above the level of the peritoneal reflection.

and from any region of perirectal spread. These specimens were transferred to bottles containing a fresh 10 per cent solution of formalin and were sectioned and stained as previously mentioned. These sections were then examined for confirmation of the grading according to the method of Broders and for typing according to a modification of the method of Dukes. Microscopic evidence of actual serosal penetration, in contrast to mere subserosal infiltration was sought. By this review, 6 cases were eliminated because of a previous error in grading them as grade 2 which left 131 cases in the final group.

The method of typing employed was a slight modification of the Dukes method (5). The criteria employed were as follows: type A, lesion limited to the mucosa; type B_1, lesion extended into the muscularis propria but did not penetrate through it; type B_2, lesion penetrated through the muscularis propria and type C, lesion of either type B_1, or B_2, with involvement of lymph nodes.

TABLE I.—COMPARISON OF FIVE YEAR SURVIVAL RATES IN CASES OF CARCINOMA SITUATED ABOVE AND BELOW THE LEVEL OF THE PERITONEAL REFLECTION

Site of lesion	Patients studied*	Patients traced	Lived 5 or more years after operation	
			Patients	Per cent of traced patients
Above the peritoneal reflection	62	57	31	54.4
Below the peritoneal reflection	69	64	38	59.4

*In this and all subsequent tables, inquiry was as of January 1, 1946. In all instances, operation was performed in 1940 or earlier.

The clinical history and the follow-up correspondence in all cases were reviewed. The cases were separated into two groups, one in which the lesions were located above the level of the peritoneal reflection and the other in which the lesions were located below this level. The data thus obtained were compared.

ANATOMIC CONSIDERATIONS

The sigmoid colon is covered by peritoneum except for the narrow mesenteric attachment low in the sigmoid colon. This mesenteric attachment gradually becomes broader and in the region of the sigmoid-rectal junction may occupy nearly half the circumference of the intestinal wall. Because of this, the upper portion of the rectum is devoid of peritoneal covering on its posterior surface, while the lateral and anterior surfaces are covered with peritoneum (4, 10, 12).

TABLE II.—COMPARISON OF FIVE YEAR SURVIVAL RATES IN CASES OF CARCINOMA SITUATED ABOVE AND BELOW THE PERITONEAL REFLECTION ACCORDING TO TYPE (DUKES) OF LESION

Type	Lesions above the level of the peritoneal reflection				Lesions below the level of the peritoneal reflection			
	Patients studied	Patients traced	Lived 5 or more yr. P. O.		Patients studied	Patients traced	Lived 5 or more yr. P. O.	
			Patients	Per cent of traced patients			Patients	Per cent of traced patients
A	1	0			1	1	1	100.0
B_1	5	4	3	75.0	8	8	6	75.0
B_2	22	20	14	70.0	36	33	23	69.7
C	34	33	12	36.4	24	22	8	36.4

TABLE III.—CARCINOMAS 5, 6 OR 7 CENTIMETERS ABOVE ANAL MARGIN: FIVE YEAR SURVIVAL RATES

Site of lesions	Patients studied	Patients traced	Lived 5 or more years after operation	
			Patients	Per cent of patients traced
Above the peritoneal reflection	20	16	7	43.8
Below the peritoneal reflection	14	14	6	42.9

At a variable level, the peritoneum is reflected off the lateral surfaces of the rectum to the sides of the pelvis and from the anterior surface of the rectum to the bladder in the male and to the posterior vaginal wall in the female (12). The anterior reflection is of course higher in the male than in the female and is at a variable height from the anal margin in both.

The level of the peritoneal reflection is an arbitrary point to a certain extent. This is inevitable because of the anatomic features previously mentioned, which are illustrated in Figure 1. It seemed wise in this study to consider the point of lateral reflection of the peritoneum to the pelvic wall as the "level" of the peritoneal reflection, although in many instances the peritoneum did dip lower than this on the anterior surface of the rectum. This lateral reflection was, in nearly every instance, definite and its site could be identified easily. Its employment as the level of peritoneal reflection gave results which could be reproduced accurately.

In the specimens studied, this level of peritoneal reflection was from 5 to 10 centimeters above the anal margin, which is in good agreement with the classic description of this region (10).

RESULTS

Of the patients traced who had lesions above the level of the peritoneal reflection, 54.4 per cent survived 5 years or more after operation and 59.4 per cent of those whose lesions were below the level survived 5 years (Table I). Both groups of patients had undergone combined abdominoperineal resection. The difference in the 5 year survival rates is probably not significant, and thus the prognosis in the entire series of cases in which the lesion is located above the level of the peritoneal reflection is entirely comparable to that in cases in which it is below it.

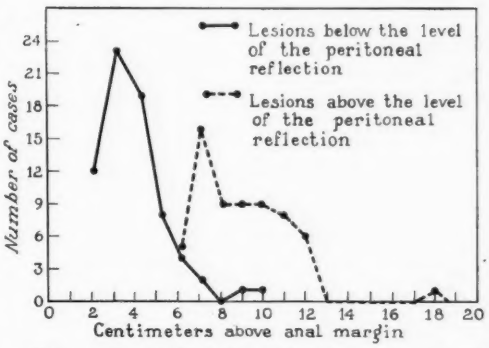


Fig. 2. Site of the lesion with reference to the anal margin in the two groups of cases studied.

In Table II are presented the 5 year survival rates of the groups of patients with lesions above and below the level of the peritoneal reflection broken down according to the slight modification of the Dukes method of typing previously described. It is apparent from these data that type for type the prognosis in cases in which the lesions are above the level of the reflection is entirely comparable with the prognosis when the lesions are below the reflection. This is further strong evidence to support the conclusion derived from this study that the location of the lesion with reference to the peritoneal reflection has no effect on the prognosis.

Before this conclusion was accepted, it had to be established with as much certainty as possible that variation in location of the lesions in the two groups with reference to the anal margin, did not influence the results. In order to establish this point, the data were analyzed further.

The distance from the lower edge of the lesions to the anal margin, as measured in the fixed specimens, in the two groups of cases is shown in Figure 2. Because of the marked variation in the level of the peritoneal reflection from the wall of the low part of the sigmoid colon and rectum, as previously mentioned, there was some overlapping be-

tween the two groups at certain levels. Thus some of the lesions, situated 5, 6, and 7 centimeters above the anal margin, were completely above the peritoneal reflection and others were completely below it. Due to this fortunate occurrence, it was possible, in a small group of cases in which the lesions were at essentially the same level in the rectum, to compare the prognosis when the lesions were located above the reflection with that in cases in which they were located beneath it. As shown in Table III, such a comparison indicated that there was no significant difference in the 5 year survival rate in the two groups. This observation substantiates the conclusion that the location of the lesion with respect to the level of the peritoneal reflection does not affect prognosis following radical combined abdominoperineal resection for carcinoma of the rectum and lower part of the sigmoid colon.

It should be noted that there is no justification for drawing conclusions as to the significance of the relatively low survival rate in cases in which lesions were 5, 6, and 7 centimeters from the anal margin. The method employed in selecting the cases for this study controlled factors pertinent to this analysis but did not control factors pertinent to a study of the effect of the level of the lesion on prognosis. An investigation of this effect is being made at present.

COMMENT

The present difference of opinion as to the surgical procedures of choice in dealing with carcinoma of the lower part of the sigmoid colon and rectum makes necessary the accumulation of all possible pertinent data. It is, of course, true that when each procedure has been carried out a significant number of times in comparable cases, and the patients have been followed for a period long enough to insure reliable survival rates, a comparison of these rates will give a reasonable insight into the relative efficacy of these procedures.

However, the difficulties inherent in the comparison of statistical material obtained from different sources in the literature are well known. Operability rates, operative mortality rates and types of lesions, as well as the location of lesions, all influence the over-all 5 year survival rate and all are rarely given in the reports. Furthermore, unless the series are actually comparable in all respects and all factors which may produce variation in prognosis in and of themselves are controlled, comparison of different statistical analyses is valueless. For example, the comparison of the 5 year survival rates after anterior resection with those after combined abdominoperineal resection is valid only if the groups of cases in which these two procedures have been employed are entirely comparable. Obviously, to begin with, the investigator must be certain that the 5 year survival rate in cases in which the lesions are high in the rectum or low in the sigmoid colon (that is, lesions suitable for anterior resection) and are removed by combined abdominoperineal resection is entirely comparable to that for the entire group treated by abdominoperineal resection. If the survival rate in cases of high-lying lesions is better after combined abdominoperineal resection than is the survival rate in cases of low lesions after the same procedure, then the 5 year survival rate following anterior resection must be compared not to that for the total group of patients treated by combined abdominoperineal resection, but to that of the patients who had lesions at the same level as those treated by anterior resection.

Thus, in order to compare statistical data obtained from the various operative procedures, with regard to survival rates alone, the data must be as complete as possible on the factors affecting the prognosis. Furthermore when these factors in prognosis are recognized and the manner of growth and spread of such lesions are understood, the surgeon can feel more secure in adopting a particular method of surgical management without awaiting the accumulation of data in sufficient quantity to give survival rates of undoubted significance.

It has been clearly demonstrated (14) that the microscopic appearance of the carcinomatous cells, reflected in the Broders system of grading, is one factor which must be considered and controlled in comparing statistical results. The choice of a surgical pro-

cedure in a given case is rarely influenced by this factor, however. The type of the lesions, according to the Dukes method of typing, is of prognostic significance (6) and must be controlled in comparisons of statistical data; again, this is rarely known preoperatively, and thus unfortunately is of little value to the surgeon in choosing an operative method in a given case (9). It is probable that the location of lesions in the rectum and lower part of the sigmoid colon, with reference to their distance from the anal margin, exerts an influence on prognosis. It is then one further factor which must be controlled in comparisons of statistical data and which must be taken into account in the choice of the surgical procedure to be employed in a given case. The method of lymphatic spread is of utmost importance in the choice of an operative procedure (8), but since it is relatively constant for lesions in the same location, it is not a factor that need be controlled in comparisons of statistical data provided the previously discussed factor of location is controlled.

Since some lesions of the rectum and lower part of the sigmoid colon lie above the level of the peritoneal reflection and some lie below this level, the relation of the lesion to the peritoneal reflection is a further factor which should be understood with reference to prognosis, and with reference to the selection of a curative operative procedure. It is demonstrated in this study that the location of the lesion with reference to the level of this peritoneal reflection has no effect on prognosis.

Thus in comparisons of statistical material and in the selection of an operative procedure in a given case, this factor may be ignored.

REFERENCES

1. BACON, H. E. Am. J. Surg., 1946, 71: 728-742.
2. BRODERS, A. C. Minnesota M., 1925, 8: 726-730.
3. DIXON, C. F. Surgery, 1944, 15: 367-377.
4. DRUECK, C. J. Med. Rec., 1920, 98: 900.
5. DUKES, C. E. J. Path. Bact., Lond., 1932, 35: 323-332.
6. Idem. Proc. R. Soc. M., Lond., 1943, 37: 131-144.
7. GILCHRIST, R. K., and DAVID, V. C. Ann. Surg., 1947, 126: 421-435.
8. GLOVER, R. P., and WAUGH, J. M. Surg. Gyn. Obst., 1946, 82: 434-448.
9. GORDON-WATSON, CHARLES. Lancet, Lond., 1938, 1: 239-245.
10. GRAY, HENRY. Anatomy of the Human Body. 24th ed., p. 1203. Philadelphia: Lea & Febiger, 1942.
11. MAHORNER, HOWARD. Ann. Surg., 1946, 123: 866-876.
12. MORRIS, HENRY. Morris' Human Anatomy; a Complete Systematic Treatise. 10th ed., pp. 1325-1326. Philadelphia: The Blakiston Co., 1942.
13. MURRAY, GORDON. Surg. Gyn. Obst., 1946, 82: 283-289.
14. RANKIN, F. W., and BRODERS, A. C. Surg. Gyn. Obst., 1928, 46: 660-667.
15. WANGENSTEEN, O. H. Surg. Gyn. Obst., 1945, 81: 1-24.

CARCINOMA OF THE ENDOMETRIUM IN YOUNG WOMEN

HAROLD SPEERT, M.D., New York, New York

NO woman, regardless of age, is immune to uterine cancer. Carcinoma of the cervix, although rare in young girls, is fairly common in women of 40 or younger. At the Roosevelt Hospital 27 per cent of all patients with cancer of the cervix were under 41 years of age. Cancer of the corpus, on the other hand, is regarded as extraordinary in women of this age group. Donald and Shaw (1929) have expressed the opinion that, "with the rarest exceptions, cancer of the body of the uterus does not begin in subjects under 40 years of age, or, alternatively, until after the retrogressive changes of the menopause have set in." Present experience, however, suggests that even fundal neoplasms in young women may be not so rare as is generally believed. The literature contains numerous references to individual cases of cancer of the corpus in children (Hirst, 1929; Kehrer and Neumann, 1929; Gilbert, 1932; Lockhart, 1935), young girls (Smith, 1933; Mazzola, 1938; Healy and Brown, 1939; Morrin and Max, 1939), and women in their early thirties (Purdie, 1945; Bianchi, 1946; Taylor and Becker, 1947; Driessen, 1947). In a recent tabulation of 255 cases of primary carcinoma of the endometrium 12 patients (4.6 per cent) were under age 41 (Speert, 1948). Two additional cases of cancer of the corpus in young women which have come to light since then make our incidence of women with this disease in the first 4 decades of life about 5 per cent. These 14 cases form the basis of the present report.

Some of the salient clinical and pathological features of the cases are summarized in Table I. From their study emerges evidence in support of the theory that continuous and unopposed estrogenic stimulation is a factor in the pathogenesis of endometrial carcinoma.

Fertility. The group as a whole showed a remarkably low degree of fertility. Eight of the patients (57 per cent) had never borne children. This percentage is slightly higher than the incidence of nulliparas among all our patients with endometrial carcinoma (41 per cent). The average parity of the 14 patients was only 0.57, in comparison to 1.34 for all patients with cancer of the corpus and 2.83 for those with cancer of the cervix. It is a striking fact that although all 14 patients were of child-bearing age, the most recent pregnancy among them had occurred 14 years previously.

Ovaries. Description of the ovaries is based on restudy of the histologic sections when available; in the other cases, on the recorded pathological reports. In 8 cases the ovaries were described as "cystic," in 1 as "sclerotic," and in 1 as "hyaline." Routine sections of the majority of the ovaries contained no evidence of ovulation. In only 2 cases were recent corpora lutea seen. Counseller (1938) has also been impressed with this negative correlation, stating that he had never seen a carcinoma of the fundus in which there was not also a failure or inactivity of the corpus luteum. An interesting feature, present in several of the present cases, was an unusually thick, tough, fibrous tunica albuginea (Figs. 2 and 5). This may possibly have acted as a mechanical barrier to ovulation, as suggested by Babes (1924) and others. Theca cell hyperplasia was described in 1 case. Two patients had had an ovary removed previously because of benign cysts.

Endometrium. The uninvolved parts of the endometrium reflected the absence of luteal activity. In no instance was a secretory type of endometrium encountered. This differs sharply from the experience of Jones and Brewer (1941) who described a secretory endometrium in 8 of 19 premenopausal patients with fundal carcinomas. On the contrary, endometrial hyperplasia was present in at least 5 of our patients. In 1 instance (Case 3) hyperplasia was probably of long standing, since it had also been diagnosed by curettage 6 years before. Another patient (A. C., Table I) had had treatment with intrauterine radium 16 years previously because of functional bleeding which

From the Gynecological Service of the Roosevelt Hospital.

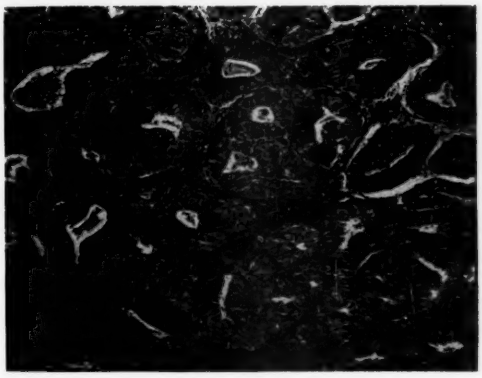


Fig. 1. Case 1. Adenocarcinoma in hyperplastic endometrium of patient aged 33 years.

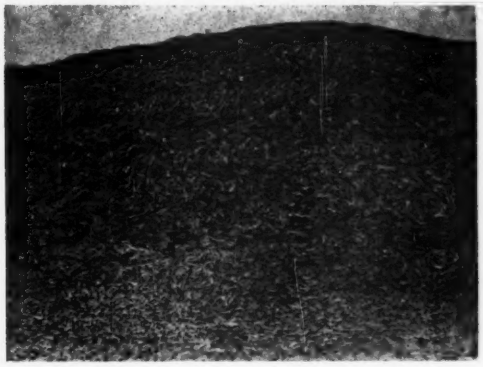


Fig. 2. Case 1. Section of ovary, showing thick, fibrous tunica albuginea.

was associated with endometrial hyperplasia.

Cervix. Squamous metaplasia resulting in epidermidization of the endocervical glands was seen in routine sections of 5 of the removed cervices. Since 2 cervices were not described, 1 was not removed, 1 was invaded by the endometrial tumor, and 1 showed a radiation reaction, the incidence of cervical epidermidization in the 9 remaining cases was 56 per cent. The possible significance of this lesion as a manifestation of abnormal estrogenic stimulation has been discussed in another paper (Speert, 1948).

Three cases, reported herewith in detail, exemplify the combination in young women of endometrial hyperplasia, endometrial carcinoma, cystic ovaries with thick tunics and no corpora lutea, and epidermidization of the cervix.

Case 1. F. W., a 33 year old, colored nulliparous divorcee, was admitted to the hospital on February 6, 1947, for curettage because of menorrhagia. Her menses had always been irregular, long periods of amenorrhea, up to a year, alternating with periods of bleeding lasting a week to a month. Her last flow occurred in mid-December 1946; the current flow began January 16, 1947. Examination was negative. Basal metabolic rate was −16. Uterine curettings showed endometrial hyperplasia and adenocarcinoma, grade 1 (Fig. 1). On February 11 total hysterectomy and bilateral salpingo-oophorectomy were performed. The ovaries were large, white, and smooth, and each was encased in a tough, thick tunica albuginea (Fig. 2). Immediately subjacent to this capsule were numerous small follicular cysts. There was no histologic evidence that either ovary had ever ovulated. Section of the cervix showed epidermidization of the glands (Fig. 3).

This is an excellent example of polyhormonal amenorrhea (Zondek, 1934) alternating with periods of menorrhagia. The associated hyperplasia of the endometrium, a presumably long-standing response to continuous, unopposed estrogenic stimulation, was the apparent forerunner of a grade 1 adenocarcinoma.

Case 2. M. H., a 22 year old, white single patient of Dr. William P. Healy, had suffered for several years with irregular intermenstrual bleeding. Various types of endocrine therapy had failed to control this bleeding. Curettage on June 13, 1944, produced a profusion of tissue which was diagnosed as hyperplasia. The patient's periods became regular for 8 months. Intermenstrual bleeding then returned, occurring daily for about 3 months prior to her readmission on January 8, 1947. Another curettage again brought forth voluminous scrapings. Diagnosis this time was endometrial hyperplasia and adenocarcinoma, grade 1. When the section of the original curettings was now reviewed a similar type of car-

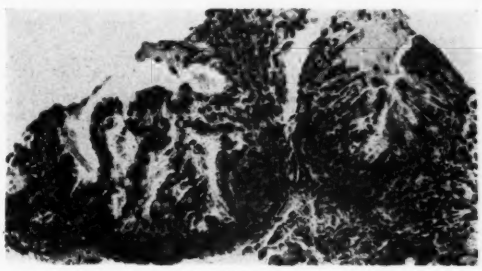


Fig. 3. Case 1. Epidermidization of cervical glands.

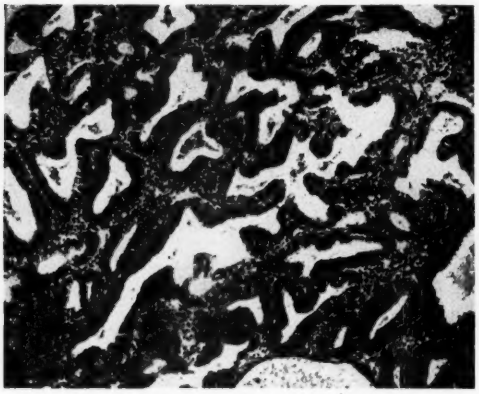


Fig. 4. Case 2. Adenocarcinoma in hyperplastic endometrium of patient aged 22 years.

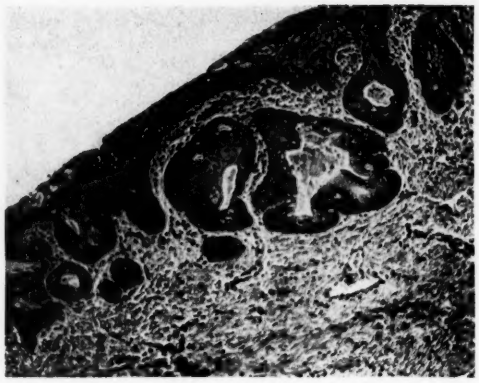


Fig. 6. Case 2. Microscopic section also showed epidermidization of cervical glands.

cinomatous change was discovered. The gross and microscopic findings in the endometrium (Fig. 4), ovaries (Fig. 5), and cervix (Fig. 6) of this patient were similar to those in Case 1.

This case illustrates the importance of investigating by curettage abnormal bleeding, even in young women, before resorting to hormonal therapy. Scheffey, Farell, and Hahn (1945) have reported 7 cases in which uterine cancer was overlooked because estrogens were used for irregular bleeding without preliminary curettage. Our recent records include several additional cases in which the same error was committed.

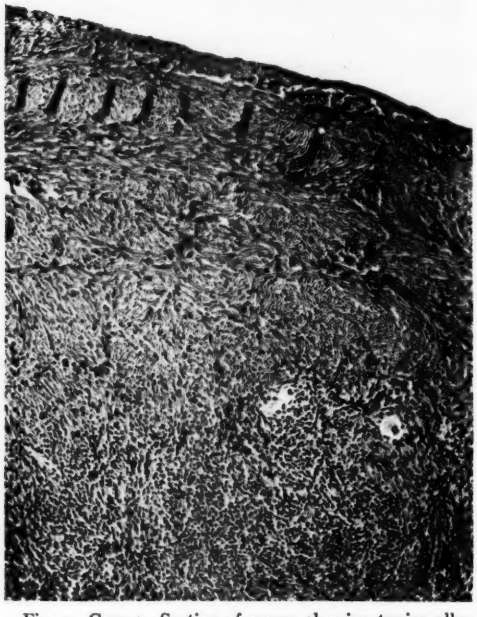


Fig. 5. Case 2. Section of ovary, showing tunica albuginea.

CASE 3. C. M., a tremendously obese (260 pounds), 37 year old white woman with a child of 14 years, was admitted February 10, 1947, because of menometrorrhagia. For 2 years her periods had lasted 10 to 14 days and for the past 6 weeks an irregular flow was observed every 1 to 4 days. Curettage had been performed 6 years previously for the same type of complaint with the curettings showing atypical hyperplasia. Curettage was repeated on February 12, 1947. Pathological report on the scrapings was endometrial hyperplasia with early carcinoma. The uterus and adnexa were removed a week later. The ovaries were cystically enlarged to a maximum diameter of 7 centimeters. Their tunics were smooth, tough, and fibrous, and measured up to 4 millimeters in thickness. There was no anatomical evidence of recent ovulation. Section of the endocervix showed epidermidization of the glands.

This case is a further example of carcinomatous change in a pre-existing hyperplastic endometrium. The interval of almost 6 years between the 2 curettings indicates the slowness of the malignant transformation. In another case (A. C., Table I), a patient of 37, 16 years had elapsed between the original diagnosis of hyperplasia and the subsequent detection of adenocarcinoma. Mazzola (1938) has also re-

TABLE I.—CARCINOMA OF ENDOMETRIUM IN PATIENTS AGED 40 AND UNDER

Patient	Race	Age	Parity	Last pregnancy	Ovaries	Cervix	Remarks
C. M.	W	37	1	14 years	Cystic, no C.L.	Epidermidization	Endometrial hyperplasia for 6 years
F. W.	C	33	0		Cystic, no C. L.	Epidermidization	Endometrial hyperplasia
M. H.	W	22	0		Cystic, no C.L., theca cell hyperplasia	Epidermidization	Endometrial hyperplasia, tubal endometriosis
A. C.	W	37	0		Cystic, no C.L.	Epidermidization	Hyperplasia previously
M. C.	W	36	1	14 years	Cystic, corpus albicans	Reported normal	Ovarian cystectomy 12 yrs.
A. R.	W	24	0		Not removed	Radiation reaction	Preoperative irradiation
G. C.	C	34	0		Cystic, no C.L.	Not described	
M. C.	W	39	2	18 years	Cystic, corpus albicans	Reported normal	Rectal cancer 9 yrs. later
E. H.	W	40	0		Recent C.L.	Normal	
R. F.	W	40	2	18 years	Cystic, corpus luteum	Not removed	Endometrial hyperplasia
A. G.	W	38	1	16 years	Tumor	Tumor	
A. A.	W	39	1	17 years	"Sclerotic"	Reported normal	Endometrial hyperplasia
C. V.	W	39	0		"Hyaline," no C.L.	Epidermidization	
E. S.	W	35	0		Tumor	Not described	Ovarian cystectomy 10 mos.

C. L., corpora lutea

ported a case of endometrial carcinoma in a young girl 12 years after the first of several curettages and radium applications for recurrent hyperplasia.

DISCUSSION

This paper is designed to emphasize three main points. First, carcinoma of the endometrium, although typically a disease of middle age, is not as rare in young women as is generally believed. Approximately 5 per cent of all cases of cancer of the corpus at the Roosevelt Hospital have been in women not over 40 years old. The second point is a corollary to the first. Abnormal uterine bleeding not associated with pregnancy merits curettage, in addition to any other type of investigation, regardless of the patient's age. Not only will an occasional, unsuspected uterine carcinoma be discovered in young women in this manner, but curettage alone affords temporary or permanent cure in many cases of functional bleeding. Hormonal therapy without preliminary curettage is unsound. Finally, the cases which form the basis of this report suggest that women who develop endometrial cancer within the first 4 decades of life conform in general to a specific hormonal pattern characterized by long continued and unopposed estrogenic activity. This is indicated by their low fertility and the high incidence among them of endometrial hyperplasia, cystic ovaries with no evidence of recent ovulation, and epidermidization of the cervical glands.

A recent study by Novak and Rutledge (1948) has called attention to certain atypical benign lesions of the endometrium, sometimes encountered in young women, which may simulate adenocarcinoma. In the light of their work one might naturally ask whether the cases herein reported were instances of genuine cancer. Only 1 of our patients is known to have died of the disease. In another, metastatic tumor was present in the ovaries. In the remaining dozen cases the diagnosis rested on the opinion of the pathologist, corroborated in a few instances by consultation with another pathologist. Recent restudy of the sections has substantiated the original diagnosis in each instance.

SUMMARY

1. Fourteen cases of endometrial carcinoma in women 40 years of age or under are reported. About 5 per cent of all corpus cancers at the Roosevelt Hospital were in this age group.

2. These cases were characterized by a high incidence of infertility, hyperplasia of the endometrium, cystic ovaries without recent ovulation, and epidermidization of the cervical glands.

3. Continuous unopposed estrogenic stimulation is an important factor in the pathogenesis of endometrial carcinoma.

4. Persistent abnormal uterine bleeding deserves curettage, regardless of the patient's age.

REFERENCES

1. Babes, A. A. Arch. Gyn. Berl., 1924, 122: 448–468.
2. Bianchi, P. Rev. ost. gin., 1946, 1: 113-126.
3. Counseller, V. S. Am. J. Obst., 1938, 35: 395–403.
4. Donald, A., and Shaw, W. F. Proc. R. Soc. M., Lond., 1929, 22: 307–314.
5. Driessen, L. D. Ned. tschr. verlosk., 1947, 47: 157-164.
6. Gilbert, J. B. Am. J. Obst., 1932, 24: 402–405.
7. Healy, W. P., and Brown, R. L. Am. J. Obst., 1939, 38: 1–10.
8. Hirst, B. C. Am. J. Obst., 1929, 18: 104–105.
9. Jones, H. O., and Brewer, J. I. Am. J. Obst., 1941, 42: 207–217.
10. Kehrer, E., and Neumann, H. O. Mschr. Geburtsh. Gyn., 1929, 81: 68–85.
11. Lockhart, H. A. Am. J. Obst., 1935, 30: 76–80.
12. Mazzola, V. P. Am. J. Obst., 1938, 36: 698–761.
13. Morrin, K. C., and Max, P. F. Surg. Gyn. Obst., 1939, 68: 30–33.
14. Novak, E., and Rutledge, F. Am. J. Obst., 1948, 55: 46–63.
15. Purdie, A. W. J. Obst. Gyn. Brit. Empire, 1945, 52: 575–579.
16. Scheffey, L. C., Farell, D. M., and Hahn, G. A. J. Am. M. Ass., 1945, 127: 76–79.
17. Smith, A. A. Nebraska M. J., 1933, 18: 19–20.
18. Speert, H. Cancer, 1948, 1: No. 4.
19. Taylor, H. C., Jr., and Becker, W. F. Surg. Gyn. Obst., 1947, 84: 129–139.
20. Zondek, B. Acta obst. gyn. scand., 1934, 13: 309–314.

EVALUATION OF THE VARIOUS CLINICAL SIGNS OF THROMBOPHLEBITIS AND EXPERIENCE IN THERAPY WITH ANTICOAGULANTS

DAVITT A. FELDER, M.D., Minneapolis, Minnesota

ALL patients with thrombophlebitis of the lower extremities in the University of Minnesota Hospitals from May, 1945 to January, 1948, have been personally examined and followed by the author. These 92 cases represent 105 extremities with deep thrombophlebitis and in some instances with superficial thrombophlebitis as well. The majority of these patients were treated with anticoagulants. We believe that the bland and the inflammatory venous thromboses of the lower extremities may practically all be called thrombophlebitis. In our hospital for the period of our study the incidence of thrombophlebitis was 92 cases in a total of 14, 116 or 0.65 per cent.

DIAGNOSIS

This study is in part an attempt to evaluate the usual diagnostic signs and symptoms of thrombophlebitis of the lower extremities. In order to be reasonably sure of the diagnosis of thrombophlebitis we have included in this report only those cases in which at least three of the following signs and symptoms were present: swelling, vessel tenderness, pain, increased temperature in the limb, dilated superficial veins (unilateral), cyanosis (unilateral), pulmonary embolism (reasonably proved), and change in temperature and pulse (otherwise unexplained). Those cases, in which unilateral swelling alone was found or pulmonary embolism alone without leg symptoms, were followed but not included in this series. In 3 instances, patients with pulmonary embolism alone developed symptoms of thrombosis in 4 to 5 days and so were included in the study.

Swelling was the most frequent symptom in this series. It occurred in 93 or 88.5 per cent of the extremities. It was accompanied by tenderness in 60 extremities and by heat in only 42 instances. Swelling, heat, and tenderness occurred in 35 extremities. In most instances, swelling was quite apparent but in some cases could be determined only by measurement. Swelling of the genitalia usually occurs when there is involvement of the common iliac vessels occluding the hypogastric vein or higher. There were 6 instances of swelling of the genitalia. In 3 instances involvement of the iliac vessels was proved at postmortem examination.

Tenderness was the symptom next in frequency to swelling. It occurred in 79, or 75 per cent, of the extremities.

Deep calf tenderness is elicited by pressing between the gastrocnemius muscle bellies in the calf (Fig. 1). It was found to be the most frequent and consistent of deep vessel signs, being present in 70 or 66.55 per cent of the extremities examined.

Calf-squeeze tenderness is elicited by gently squeezing the calf from side to side (Fig. 2). Its value has been stressed by Moses. While probably not as significant as deep calf tenderness it is an important maneuver in substantiating deep vein involvement when used with the deep calf pressure. It was found in 56 or 53 per cent of the extremities. Calf-squeeze and deep calf tenderness together occurred in 50, or 45.5 per cent, of the extremities.

Homans' sign is the presence of pain in the calf elicited by passive dorsiflexion of the foot (Fig. 3). In all of these maneuvers for deep vein tenderness, one must remember to keep the knee flexed thereby relaxing the calf muscles. This sign was found to be positive in 52, or 49.5 per cent, of the extremities. Aside from the fact that this sign is the least frequent of those mentioned here, we believe that it is much less reliable for routine examination because of the great possibility of its being positive in the presence of simple muscle involvement alone. It involves mostly muscle stretch-

From the Department of Surgery, University of Minnesota.

Fig. 1. Maneuver to elicit deep calf tenderness.

Fig. 2. Calf-squeeze maneuver.

ing and deep vein pressure only secondarily, whereas the calf squeeze and especially the deep calf maneuvers involve more direct pressure over the vessels in question (mainly the posterior tibial and calf veins where most thromboses probably begin).

Popliteal tenderness was found in only 17 instances, never without other tenderness. This would lead one to believe that it is of limited value as a diagnostic sign.

Anterior tibial tenderness was found in only 2 instances. Involvement of the anterior tibial veins in thrombosis is not frequent but has been found to be present in a number of instances. This was indicated by fairly definite venographic studies done by the author in patients with chronic deep thrombophlebitis and in a few of the cases in this series. The infrequency of anterior tibial vein involvement might be due to the fact that these vessels do not drain large venous lakes as do the posterior tibials from the calf muscle group. Frykholm has proposed that collapse of veins with contiguity of vein walls is a causative factor in thrombosis of the deep leg veins in bedridden patients. The anterior tibial vessels are protected from such pressure by their anatomical position.

In 3 cases the tenderness shifted from the calf to appear in the femoral canal area without involving the intervening popliteal area. These cases may represent the syndrome described by Homans in which a thrombus originating in the leg later attaches in the femoral region or higher and unless the vein wall between the two areas is involved with the thrombus there is no tenderness.

Profunda femoris involvement, frequently overlooked, has been emphasized by Homans. It is elicited by grasping the biceps femoris muscles and squeezing moderately. In none of the 12 patients of our series with profunda femoris tenderness was its presence the only sign of tenderness in the extremity. Though it is possible that such a thrombosis might exist alone, our observations to date indicate that its presence alone is rare.

Heat. We have found that a temperature difference of 3 to 4 degrees F. can be determined fairly consistently by simple palpation. Except for a few instances, in which an electrothermocouple was used, increased heat was determined by palpation and only definite temperature differences are included.

In 54 instances, or 53 per cent, there was an appreciable temperature increase in the affected limb. Increased heat was usually accompanied by tenderness (42 extremities) and swelling (42 extremities). However, there were many instances of swelling without heat (38 extremities). This latter figure includes the acute phlegmasias in which the limb was actually colder. Even with these cases excluded, the incidence of swelling of an extremity without heat is still fairly high (27 instances).

Pain. This symptom was present in 54 patients at rest. Many more had pain in the calf only on walking. A few described their discomfort on walking as tightness rather than pain. This symptom was noted especially in patients in whom the level of the thrombosis was high, as in the iliofemoral thromboses. These patients complained of tightness in the thigh as well as in the calf.

Color changes. The dusky color often described as a concomitant of thrombophlebitis was noted in only 4 of our cases. There were 5 extremities which were definitely redder than their mates. One of these was the case of suppurative phlebitis. In the 11 patients with phlegmasia alba dolens discussed later, the limbs were pale.

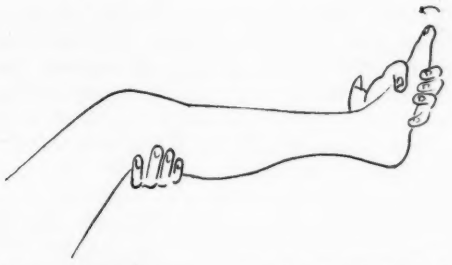


Fig. 3. Homans' maneuver of passive dorsiflexion of the foot to elicit calf pain.

Dilated superficial veins. The presence of dilated superficial veins is sometimes of use in making a diagnosis of deep vein thrombosis. This finding was noted in only 3 cases in this series. It probably is indicative of thrombosis above the common femoral when the long saphenous bears a great burden of the venous drainage or when its entrance into the femoral is also occluded, so that the pressure in it is elevated. This dilatation disappears as soon as ample additional collaterals are established; with bed rest in the Trendelenburg position and with the administration of anticoagulants, this ordinarily has taken no longer than 48 hours. From our experience with patients studied prior to this series and subsequent to it, we believe that dilatation of the superficial vessels occurs at least twice as often as recorded here.

Level of thrombosis. It has been claimed by Birger and Bauer (5) that if one could stop a thrombosis from progressing above the popliteal level, patients could be assured of a much brighter future as far as complicating factors such as persistent edema and stasis changes are concerned. An attempt was made to determine the level of thrombosis clinically. When a patient was found to have ankle or leg edema, it was thought, unless there was indicative tenderness higher, that the patient's level of thrombosis was probably the posterior tibial vein. The thrombus might extend into the popliteal vein or higher, but was probably not occluding its lumen. There were 58 such extremities, the left leg being more often involved than the right.

Sural vein thrombosis. The sural veins drain the posterior muscle group of the leg (Fig. 4).

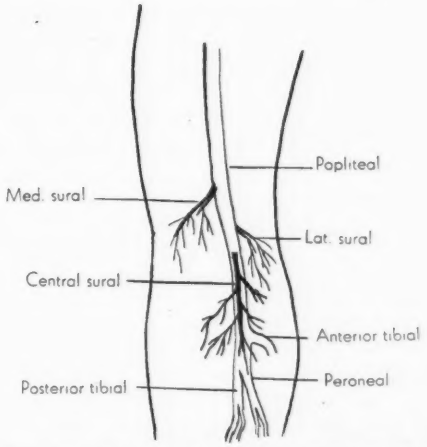


Fig. 4. Example of sural vein distribution (from dissections on amputated extremities by the author).

In 2 cases a simple sural vein thrombosis was found with surrounding induration of the calf. These thrombi can often be felt on one or both sides of the upper calf just below the knee. Sural vein thrombosis should not be treated lightly and is as important as any other deep thrombophlebitis or thrombosis, for such thromboses generally progress to involve the popliteal vein and upward. Many of our patients with deep thrombosis had induration of the calf, probably due to a blocking of the sural veins as they enter the popliteal.

There were 41 instances in which swelling of the thigh and legs usually with femoral vein tenderness up to the inguinal fold, was considered as an indication of iliofemoral thrombosis, with the thrombosis either at a femoral or external iliac level.

In the patients with swelling and tenderness above the inguinal fold into the lower abdomen and in some cases involving the genitalia (swelling), the level of the thrombus was assumed to be iliac. With swelling of the genitalia, the level was assumed to be at the common iliac with involvement or occlusion of the hypogastric.

That clinical impressions can be grossly incorrect in this disease was proved by 2 patients in whom clinically the level of the thrombosis was found to be at the posterior tibial and femoral veins, respectively. At op-

eration there was an occluding thrombus up to the level of the profunda in the former and up to the external iliac in the latter. In the latter case, it is only fair to say that there was dilatation of the entire superficial venous tree of the extremity but not above the inguinal fold.

TREATMENT

It is obvious that the treatment of venous thrombosis of the lower extremities should be directed at: (1) preventing propagation of an existing clot, (2) preventing embolization, and (3) keeping the patient as comfortable as possible both during and after such treatment. This study is an attempt to evaluate the efficacy of anticoagulant therapy in accomplishing this purpose.

At the beginning of this study it was decided that all patients with thrombophlebitis in the University Hospitals would be treated by anticoagulants with the exception of those particularly unsuited to this form of treatment by virtue of certain contraindications, such as subacute bacterial endocarditis, renal or hepatic disease, purpuric diseases, bleeding lesions, those preoperative cases when in the opinion of the surgeon anticoagulants were not desirable, or those postoperative cases when large bare bleeding surfaces were to be expected.

It was also decided that these patients would be treated with bed rest in moderate Trendelenburg position (the foot of the bed on 4 to 6 inch blocks) as soon as the diagnosis of thrombophlebitis was made. The only exceptions were patients with severe or acute cardiac disease, patients with restricted vital capacity, and those with pulmonary embolism in whom in this position pleural pain was aggravated. This method of care was prompted by the work of Bauer (5), who showed fairly conclusively that the rate of venous blood flow was increased by this position because the veins remained small and free of stasis or laking. The purpose of this procedure is to reduce to a minimum the chances of propagation of thrombi already formed and to discourage new thrombus formation further than might be done by the anticoagulants. This study was begun when the use of anticoagulants was not as well accepted as it is now and an added safety factor was thought advisable, however small its contribution may have been for the result herein reported. It is a procedure to be recommended especially when anticoagulants are not used as put forth by Homans and others even earlier. At the beginning of the study it was also decided that no patient should receive sympathetic blocks, local or reflex heat, or other forms of therapy directed at the thrombophlebitis.

One patient received repeated sympathetic blocks for concomitant or primary peripheral arterial embolism.

Heparin. Since the original work of Murray and MacKenzie and of Crafoord and Jorpes (8), heparin has come into clinical use increasingly both as a prophylaxis against primary thrombosis and as a preventative against propagation of the thrombosis already existent. The recent work of Loewe and Richter even further suggests that heparin may aid in dissolution of the early clot.

By virtue of its negative charges, heparin combines with prothrombin, thrombin, fibrinogen, and thrombokinase to prevent them from acting in their usual capacity, as shown by Jorpes (14).

This drug was used in 54 of our patients, exclusively in 8 and with dicumarol in 46. The average period of treatment for the whole group was from 2 to 8 days. The majority of patients were treated for from 1 to 2 days.

In the first 25 cases in which heparin was used this drug was given intravenously every 3 hours. A clotting time was taken as a control prior to treatment and 1½ hours after each dose. An attempt was made to keep this 1½ hour clotting time at from 2 to 3 times the control, or the patient's normal. The majority of this group required 50 milligrams of heparin intravenously every 3 hours to maintain this level of clotting time. A few patients required as much as 60 to 70 milligrams for the same effect. In 3 extremely ill patients it was found that only 20 milligrams was required for the same effect. These patients were markedly debilitated to begin with and 2 were found later at autopsy to have hepatic involvement of moderately severe degree.

On the other hand, one extremely ill patient with carcinoma of the ovary and pelvic ab-

scesses required 60 to 70 milligrams of heparin intravenously to maintain her 1½ hour clotting time at 2 to 3 times normal. The answer to this problem is not clear to us and can be theorized on at length.

The reports of the Swedish investigators, Crafoord and Jorpes (8) attracted our attention sufficiently so that we tried their dosage of 100 milligrams repeatedly during the day and 100 milligrams at midnight. Most of these cases fell into our prophylactic group (not included in this paper), but 1 patient with thrombophlebitis was so treated. It was found in this group that the clotting time at 2 hours was still between 2 and 3 times the normal and tapered down from this point instead of the 1½ hour peak of the 3 hour dosage of 50 milligrams.

A later work of Bauer (6) recommended a dosage of 50 milligrams every 4 hours during the day and 100 milligrams at midnight. Such obviously good results were obtained in his series that we decided to use this method of treatment with heparin and up to the end of this series of cases had tried this regimen in 25 cases. In this group the peak of the clotting time was usually at 1½ hours and normal again at 4 hours.

Clotting times were taken before starting heparin, then in the early cases every half hour after each dose for 2 to 3 doses. It became apparent quite early that the clotting time was down to normal within from 3 to 4 hours after each injection of 50 milligrams and well within 8 hours after the 100 milligram midnight dose. This midnight dose of 100 milligrams was used merely because we wished to give Bauer's method a fair trial. It is doubtful that this 100 milligram dose adds much to the treatment. In only 1 case in our group was the clotting time elevated 8 hours after the midnight 100 milligram dose.

For the extremely ill patient with possible liver damage one might assume from our experiences with the 3 hour dosage, that it would be dangerous to give such patients 50 milligrams. In these patients the 50 milligram dose produces an unpredictable clotting time peak but as shown by our studies with the 50 milligrams every 4 hours, the clotting time is invariably down to normal within 3 to 4 hours. In none of the heparin-treated patients was there any serious hemorrhage. This series is hardly large enough to base a final impression on, but the results are encouraging to date.

It is quite apparent that the intermittent, intravenous route of giving heparin is far from ideal although empirically of value. Loewe and his co-workers perhaps have the beginning at least of a more rational and practical method of treatment with heparin in their heparin in Pitkin's menstruum (16).

We have tried this method in 7 of our patients. In 5 cases the originally recommended dose was 300 milligrams (with vasoconstrictor). In 4 of these an adequate rise in clotting time was obtained within 12 hours and it remained elevated for 12 hours. Two of these patients required supplementary intravenous heparin every 3 hours to maintain a 1½ hour clotting time of 2 to 3 times normal until the effect of the heparin in Pitkin's menstruum became manifest.

Two patients in this group were treated with 500 milligram doses (300 mgm. with vasoconstrictor and 200 mgm. without vasoconstrictor mixed 150 mgm. plus 100 mgm. respectively in 2 portions and injected 1 into each thigh). In these cases a good response was observed within 8 hours and the clotting times remained elevated at 2 to 3 times normal for 48 hours.

Heparin is a relatively safe anticoagulant when given intravenously by intermittent doses. Although it probably detracts from the safety element somewhat, the subcutaneous route seems to be more practical. The recent studies of McCleery and Sirak with coronamid in heparin in Pitkin's menstruum to prolong the heparin effect and consequently requiring less heparin are very encouraging and may bring us to use the subcutaneous route in the majority of cases.

Dicumarol. The action of dicumarol as described by Link is primarily on the liver inhibiting its formation of prothrombin. The anticoagulant effect of dicumarol results only from the diminution in the available prothrombin usually necessary to clot formation. Its relative insolubility except in very alkaline solution limits its practical administration to the oral route. Admittedly it is a potentially

dangerous drug when its action depends on the irregularities of intestinal absorption and a special effect on the liver's prothrombin production. For these reasons one must be prepared to follow prothrombin times regularly and to combat the possible results of occasional unpredictable prothrombin depletion that may result before attempting the use of this drug as outlined below.

This anticoagulant was used in 77 of our cases. The method of dosage described by Yahr and associates and by Barker and associates was followed in essence. We gave the average patient 300 milligrams of dicumarol the first day (100 mgm. per 50 pounds of body weight); 200 milligrams the second day (two-thirds of the initial dose); and 100 milligrams on the third day (one-third the initial dose) provided the prothrombin ratio (control: patient) was not 1.5 or higher. Our second day dosage was divided into 100 milligram morning and evening doses which allowed a little longer spread of our therapeutic level of prothrombin ratio from the initial dosages. This latter factor came into more importance in the prophylactic group in which a simple postoperative dosage like this (300 mgm., 100 mgm.+100 mgm., 100 mgm.) gave a prothrombin time of 2 to 3 times the normal for 5 to 6 days without further dosage in most cases.

This divided second day dosage allowed us to stop at 400 milligrams in patients who proved to react with a significantly increased prothrombin time (1.5 times normal or more) by 24 hours after the first dose.

It took an average of 2.5 days for the prothrombin times of these patients to come to 1.5 times the normal or higher. The majority of the cases came into this range of prothrombin time within 2 days. The day after the first dose was counted as the first day. In other words, a prothrombin ratio of 1.5 or higher was obtained in most patients in from 24 to 36 hours.

In the early part of our experience with dicumarol we noticed some instances of bleeding from the mucous membranes, wounds, kidneys, etc. During this time we were keeping our prothrombin ratios between 4 and 5 times the normal. As can be expected by the curves of Quick, the prothrombin time shot to extremely high levels and in some instances the plasma could not be made to clot. In these cases vitamin K in doses of 72 milligrams intravenously was given and usually the prothrombin time returned to reasonable levels within 10 to 12 hours, and on repeating this dose (if necessary) in another 10 to 12 hours, the prothrombin time would be normal. We found also that whole blood transfusions would bring the prothrombin time down, but the longest effect we were able to demonstrate was 9½ hours, after which time the prothrombin time gradually returned to a high level. The higher the prothrombin time, the more blood it took to bring the prothrombin time back to normal. Fresh blood was much more potent in this effect than blood 24 hours old or older.

In a few cases, secondary operative procedures, such as drainage of subphrenic abscesses, were found necessary after patients had been dicumarolized. In these cases, if the prothrombin time was only between 2 and 3 times the normal, it usually sufficed to give the patient one fresh whole blood transfusion 2 to 3 hours prior to surgery and the prothrombin time was close to normal at the time of the procedure, and remained so for 8 to 9 hours and then rose again. It is only fair to mention that in 1 patient being treated prophylactically and prepared as outlined, subphrenic exploration was attended by a good deal of bleeding and the patient required another transfusion before bleeding was controlled.

We might cite the case of 1 patient with an old trimalleolar fracture requiring surgery treated for thrombophlebitis preoperatively with dicumarol until 1 week after disappearance of signs and symptoms, at which point her prothrombin time was 2.5 times the normal. She was given 128.0 milligrams of vitamin K intravenously the night before surgery and a fresh blood transfusion a few hours before surgery and went to surgery with a normal prothrombin time. Her postoperative course was uneventful.

Keeping the prothrombin ratio between 2 and 3 times the normal, rather than previous higher levels, the incidence of significant bleeding all but disappeared in this series, save

for an occasional microscopic or transient gross hematuria.

Duration of treatment. The average duration of treatment (prothrombin time of 2 times normal or above) was 14 days. In most cases the period of treatment was between 10 and 19 days.

The patients with pulmonary embolism were treated for the longest period. These comprised the group receiving between 14 and 21 days of dicumarol treatment.

Of the patients inadequately treated (only 3 to 5 days of therapy or with a prothrombin ratio not continuously between 2 and 3) only 1 died of pulmonary embolism.

We attempted to treat our patients without embolism for a period of 14 days and those with embolism for 21 days. Those without embolism were ambulated with ace bandage support as soon as all signs and symptoms were negative (usually by the seventh day) and kept under treatment until the total period of therapy was 14 days. The patients with pulmonary embolism were kept in bed for at least 10 and, in most cases, 14 days, and kept under treatment for a total period of 21 days.

Bed rest. As mentioned before, bed rest was in moderate Trendelenburg position for all patients who could tolerate it. The average length of stay in bed after the onset of the phlebitis or discovery of it was 10.5 days. Most of the patients were kept in bed for 10 days or less. It is extremely difficult to decide on the proper period of bed rest. One patient experienced a nonfatal pulmonary embolism after being in bed only 4 days. Still another was allowed up only after 18 days of therapy, and 2 days after being up with a normal prothrombin time developed a pulmonary embolism.

Femoral vein ligation. Ligation of the common femoral vein was performed in 8 patients in this series for various reasons as shown in Table I. In view of the arguments concerning the possibility of involvement of the profunda vein, the incidence of undiagnosed bilateral involvement, and the anatomical points brought out by Edward Edwards (10) in his recent study, we perform bilateral ligations of the common femoral. In 1 patient, with a phlegmonous phlebitis of the saphenous parva and deep vein involvement unilateral ligation only was done. In all, a total of 15 ligations were carried out in the 8 patients.

TABLE I.—FEMORAL VEIN LIGATIONS IN 92 CASES OF ACUTE THROMBOPHLEBITIS

	Age Years	Reason for ligation
1. R. K.	18	Subacute bacterial endocarditis
2. O. F.	74	Phlegmonous phlebitis
3. I. L.	66	Preoperative gastrectomy for carcinoma with bleeding lesion
4. H. J.	64	Preoperative gastrectomy for bleeding carcinoma
5. F. E.	63	Postoperative transurethral prostatectomy
6. C. D.	77	Carcinoma of bladder postfulguration; bleeding
7. C. H.	81	Preoperative prostatectomy for carcinoma
8. W. B.	84	Repeated pulmonary embolism after two courses of dicumarol. Demonstrable phlebitis only on last attack of pulmonary embolism

TYPES OF CASES

By way of interest, we have divided our cases into bland and inflammatory types. Under bland thrombosis we included those without noticeable temperature change in the extremity and usually with less evidence of inflammation such as pain, tenderness, or redness. The so called cases of phlebothrombosis would fall into this group, however, it is admitted that according to the criteria set up at the beginning for including cases in this study, we perforce have possibly excluded some cases of so called phlebothrombosis. Thirty-seven of the patients fell into this group.

Under inflammatory thrombosis we included all the rest of the patients who of course had evidences of inflammation such as noticeable temperature elevation of the extremity, pain, tenderness, and in some instances color changes. Swelling is considered by us as a sign of venous obstruction for the most part, although accompanying lymphangitis and local tissue reaction probably play a role in many of these cases. There were 54 cases in this group.

Acute iliofemoral thrombosis. The sudden swelling of an entire lower extremity is an entity often described and probably represents the sudden involvement by a thrombus of the critical level of venous drainage just proximal

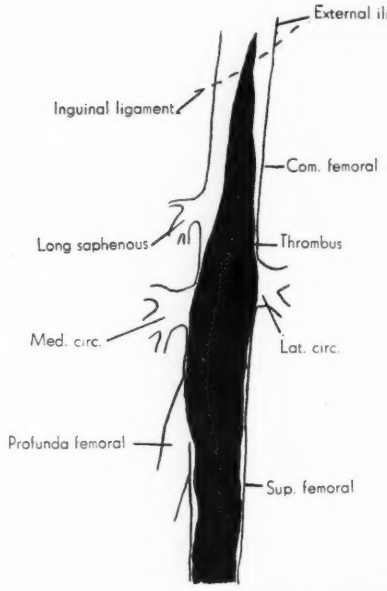


Fig. 5. Mechanism of acute iliofemoral thrombosis.

to the profunda femoris vein. At this level the profunda femoris, the lateral and medial circumflex, and a little higher the long saphenous enter the femoral vein (Fig. 5). The tail of such a thrombus and later the thrombus itself extend well into the external iliac vein; thus the term iliofemoral thrombosis. One can readily see the extent of obstruction by such a thrombus. This sudden swelling is frequently accompanied by pain and a sense of tightness in the extremity. These limbs may be warmer or cooler, duskier or paler, and the arterial pulses may be the same or less than in the opposite limb. In our series, there were 23 extremities in this category. Three of these were in patients giving a history of old iliofemoral thrombosis with a superimposed acute process.

The so called phlegmasia alba dolens of a cold, white, swollen but not always painful extremity, was seen in 11 instances. There was surprisingly little incidence of pain and almost no incidence of tenderness in these. Nine of these patients were in bed at the time of onset. In the 2 patients who were ambulatory at the time of onset there was appreciable

TABLE II.—TYPES OF VENOUS THROMBOSIS OF THE LOWER EXTREMITIES

Type	No. cases
Bland thrombosis	37
Inflammatory thrombosis	54
	91
Acute iliofemoral thrombosis	20
Old iliofemoral and acute process	3
Phlegmasia alba dolens	11
	23
Superficial thrombophlebitis	5

pain. The presence of swelling may well have accounted for the failure to elicit tenderness.

Superficial thrombophlebitis. During the course of this study 5 postoperative cases of superficial thrombophlebitis were seen and treated with anticoagulants. Two cases were associated with deep thrombophlebitis. Two patients suffered pulmonary embolism calling attention to an otherwise unrecognized thrombophlebitis. Two developed while the patients were being treated for deep thrombophlebitis. All of these patients went through the natural course of the disease unaltered.

Pulmonary embolism. There were 27 patients in this series who had pulmonary embolism. These represent 29 per cent of the entire group. This figure is a little less than the 33 per cent found for untreated cases in a similar group by Welch and Faxon and by Allen (1).

In 11 patients pulmonary embolism was the first indication of the presence of thrombosis in the veins of the lower extremities. In 3 of the patients mentioned, symptoms of deep vein thrombosis did not appear until several days after the embolism. In another 10 patients the thrombophlebitis and pulmonary embolism were noted on the same day. This means that 21, or 78 per cent, of these patients already had a pulmonary embolism by the time treatment could be begun.

It is interesting to note that 13 of the patients having pulmonary embolism were those with a supposedly bland type of thrombosis and 14 were in the group of those with an inflammatory process. This result seems contrary to the common belief that the bland

process leads to pulmonary embolism more often than the inflammatory process. We do not mean to leave this impression. An autopsy study such as Hunter's could very well show such a predominance of embolus resulting from the bland process for it includes patients who had thrombosis in the lower extremities without signs. Unfortunately we were not able to secure complete autopsies including leg dissections of fatalities in our hospital during the same period as our study. It is also to be argued that patients with nonfatal pulmonary embolism and without clinical evidence of thrombosis would not fall into a series like ours or an autopsy analysis. Therefore it is probably true that pulmonary embolism is more common with bland processes than with the inflammatory ones.

Six patients developed pulmonary embolism while actually on anticoagulant therapy. They cannot all be considered to have had adequate treatment, however. This number includes a patient who was adequately treated for 18 days with anticoagulants. Two days after her prothrombin time had returned to normal while up and around, she developed a small nonfatal embolism. After 11 more days of anticoagulant treatment she had no further trouble. This patient and one other who died were the only 2 patients who developed an embolism while treatment supposedly was adequate. The 4 remaining patients had pulmonary embolism on the first or second day after treatment was begun and so in a sense were not adequately treated. These 4 patients added to the 21 who had pulmonary embolism to begin with make 25, or 92 per cent, of this group who had pulmonary embolism before anticoagulant treatment could become effective.

There were 5 deaths in our series. In only 1 can we consider pulmonary embolism as the primary cause. All of these patients were seriously ill and, except for the 1 fatality mentioned, slowly succumbed to diseases other than pulmonary embolism. Three of these patients, however, were found to have pulmonary emboli present at autopsy but these were not thought to be the cause of death. For the evaluation of the reader, a summary of the fatal cases follows:

Patient	Hospital No.	Treatment	Autopsy findings
1. N. B.	781277	Adequate anticoagulants	Massive pulmonary embolus in carcinoma of pancreas
2. H. K.	771548	Inadequate heparin therapy stopped 5 days prior to death	Far advanced ulcerative colitis with inanition. Incidental pulmonary embolus
3. I. L.	782808	Bilateral femoral ligation preoperatively	Tension pneumothorax incidental pulmonary embolus
4. A. M.	710417	Inadequate heparin therapy stopped 4 days prior to death	Carcinoma of pancreas with generalized metastases and incidental pulmonary embolus
5. A. K.	777476	Inadequate heparin therapy stopped 5 days prior to death	Far advanced biliary cirrhosis of the liver with external biliary fistulas

According to the data presented by Welch and Faxon about 30 per cent of the patients who have one pulmonary embolus from a thrombophlebitis will have another. They also indicate that about 25 per cent of the group of patients with one embolism will have a fatal embolism. In our series there were only 2 secondary pulmonary emboli and neither of these proved fatal.

In 19 of our cases there were x-ray findings characteristic of pulmonary embolism. As can be seen by Table III, most of the emboli produced x-ray evidence on the right side and showed a preference for the lower lobes. This has been observed and commented on by Roesseler, Allen (2), and others. In some cases clinical evidence of pulmonary infarct was present in the lower lobes but was not recognized on the ordinary chest film because of interference by the diaphragm or heart shadows. In such cases roentgenograms in the lateral projection or with overpenetration are indicated in order to substantiate the diagnosis made.

TABLE III.—LOBES INVOLVED IN PULMONARY EMBOLISM AS PROVED BY X-RAY EXAMINATION

	Right		Left
Upper	3	Upper	0
Middle	4	Lower	5
Lower	11		
Total	18 (78%)		5 (22%)

23 lobes

TABLE IV.—ASSOCIATED FINDINGS WITH PULMONARY EMBOLISM IN THROMBOPHLEBITIS

	No. cases	Per cent
Bland process	14	51.8
Inflammatory process	13	48.1
Signs of thrombosis 4 to 5 days after embolus	3	11.1
Chest pain	19	70.0
Hemoptysis	15	55.5
X-ray findings	19	70.0
No x-ray findings	8	30.0
After surgery	15	55.5

Chest pain and hemoptysis. It can be seen from Table IV that a good portion (70 per cent) of the patients had chest pain and hemoptysis. Chest pain was the most common symptom. A few patients had upper abdominal pain and a few had shoulder-strap pain at the onset of the embolism. Hemoptysis began usually within the first 24 hours after the embolism. An occasional patient did not cough up bloody sputum for several days and others had cough without sputum, and some neither cough nor sputum.

Hemorrhagic manifestations. It can be seen from Table V that except for patient A.K., all of the patients in this series who had hemorrhagic manifestations were those on dicumarol and with a prothrombin ratio of 4 or over. These cases prompted us to lower our period of treatment with dicumarol. In patients in the latter half of our series and to date, we have endeavored to keep the prothrombin ratio below 4 and preferably between 2 and 3. After this change in our form of treatment we noted a marked decrease in hemorrhagic manifestations with only an occasional transient hematuria or hemorrhagic skin lesion.

Hematuria. Except for patient S. R., upon whom a posttransurethral prostatectomy was performed, the urinary bleeding was not a source of concern in this group even though grossly visible in 8 cases. In all except patients S. R. and H. M., no change was made in the treatment and no special measures were taken to stop the bleeding. In all of these latter instances hematuria cleared up spontaneously within 3 days. Within 24 hours after disappearance of gross blood and in most instances sooner, no microscopic evidence of blood could be found in the urine. This observation was checked by examination of separate urine specimens every 4 hours after the onset of gross hematuria. At first the patients with microscopic hematuria were checked only daily and as soon as the findings were negative examination was made only every 2 days. All of our patients had a routine urinalysis every other day. In no instance was microscopic hematuria reported prior to a pink or red urine being observed grossly. These findings have been noted in our prophylactic series also, and suggest that dicumarol therapy might in some way at least be responsible for one or more small renal arteriolar or even capillary accidents from which recovery is rather rapid even when the patient is continued on the treatment. We have observed that some other patients treated with dicumarol had multiple episodes of transient hematuria.

Skin manifestations. Peculiar hemorrhagic skin lesions in our patients treated with dicumarol were observed. These lesions were accompanied by a burning pain and extreme tenderness. We have seen 4 lesions (2 appearing in this series as shown in Table V) which suggested a resulting necrosis but all healed spontaneously within 10 days. Here again, as in the transient hematuria, one might easily postulate some small arteriolar or capillary damage somehow related to dicumarol therapy.

No other skin lesions have been noted in our dicumarol-treated patients suggestive of sensitivity or toxicity attributable to dicumarol.

PRIMARY CONDITION

To correlate the incidence of thrombophlebitis with various other conditions, an analysis of the primary diagnoses for which the patients were in the hospital was made. Other associated factors such as operations and in some cases other concomitant diseases were analyzed.

Thrombophlebitis. In 9 patients or 10 per cent, deep thrombophlebitis was the primary disease. A careful historical and physical re-

TABLE V.—HEMORRHAGIC MANIFESTATIONS IN PATIENTS ON ANTICOAGULANT THERAPY FOR THROMBOPHLEBITIS

Patient	Hosp. No.	Anti-coag-ulant used	Hematuria duration		Purpuric manifestations			Gastro-intes-tinal	Mucous mem-brane	Uterine	Remarks
			Days								
			Gross	Micro	Hema-toma	Toxic erythema	Ecchy-mosis				
P. F.	773651	D	1	1							128 mgm. vitamin K. 1 transfusion.
S. R.	768639	D	7	8					Gums 3 days		Posttransurethral prostatectomy. Six transfusions 300 mgms. vit. K. Liver function O. K.
M. W.	782940	D			Butt-ocks						Cleared up spontaneously.
R. N.	768695	D						Rectum 2 days			Polio case. 60 mgms. vit. K. Liver function O.K.
T. N.	771268	D	4	4						Menses 3 days	Polio case. Cleared up spontaneously.
H. K.	777548	H						Rectum 10 days	Gums & nose 10 days		Biliary cirrhosis. Heparin discontinued but bleeding continued. Not serious.
E. G.	775299	D								Menses 5 days	No treatment.
O. S.	746851	D	2	2							Cleared up without treatment
F. A.	772605	D	3	3				Ileos-tomy 5 days			Regional enteritis, post resection and ileostomy. No treatment.
H. M.	777982	D	2	?							60 mgm. vit. K. Hematuria persisted for more than a week. Postfulgur-ation bladder carcinoma.
E. D.	772624	D				Thigh					Cleared up spontaneously.
A. K.	777476	H							Gums?		Heparin stopped 5 days ante mortem. Extremely ill ulcerative colitis case.
O. F.	670645	D	2								Cleared up spontaneously.
H. W.	77128	D	1	1	Elbow						Ten days post partum. Cleared up spontaneously.
J. D.	772371	D				Thigh					Cleared up spontaneously.
J. W.	642109	D					Leg				Cleared up spontaneously.
E. N.	601863	D			Sub-phrenic						Infected hematoma in drained sub-phrenic abscess. Necrosis of liver at post mortem.

view of systems revealed no other significant concomitant disease. On the other hand, Miller and Rogers reported a primary diagnosis of thrombophlebitis in 30 per cent of their patients, a series similar to ours in numbers at least.

Cancer. The high incidence of thrombophlebitis in patients with cancer has long been noted (19) and is seen in our study also. The reason for this is not yet fully apparent. In patients with thrombophlebitis one should always suspect and look for a neoplastic process when there is no apparent causative factor for the thrombosis. In 1 of our cases it was not until postmortem examination that a carcinoma of the pancreas was found.

Cancer was a concomitant or primary disease in 38 of our patients. Of these, 14 had not been operated upon. The relatively higher

TABLE VI.—CANCER IN 92 CASES OF THROMBOPHLEBITIS

	No. cases
Stomach	9
Large bowel	7
Ovary and uterus	7
Prostate	4
Bladder	3
Breast	2
Pancreas	2
Tongue	1
Brain	1
Small bowel	1
Lung	1
Total	38

TABLE VII.—POSTOPERATIVE THROMBOPHLEBITIS IN 92 CASES OF THROMBOPHLEBITIS OF THE LOWER EXTREMITIES

Operation	Total Operations	Thrombophlebitis Number	Thrombophlebitis Per cent
Gastric resection cancer	497	9	1.8
cancer	163	6	3.6
Colon resection	353	6	1.7
cancer	185	5	2.6
Hip fixation	60	4	6.6
Hysterectomy	74	4	5.4
cancer	31	4	12.8
Prostatectomy	451	4	.88
Cholecystectomy	181	3	1.65
Hernia	169	3	1.77
Amputation	88	3	3.4
Colpoperineoplasty	51	3	5.8
Dilatation and curettage	192	2	1.04
Small bowel resection	70	2	2.9
cancer	4	1	25.0
Bladder resection (all cancer)	7	2	28.0
Radical mastectomy	88	2	2.3
Pneumonectomy	12	1	8.3
cancer		1	
Colostomy closure	16	1	6.3
Shoulder manipulation		1	
Craniotomy	144	1	.69
cancer		1	

incidence of thrombophlebitis in postoperative cancer patients as compared with noncancer patients is shown in Table VII.

The comparatively high number of cases of gastrointestinal, gynecological, and genitourinary cancer in this series (Table VI) is due to the fact that our hospital receives an inordinate number of cases of gastrointestinal cancer and gynecological and genitourinary cancer, compared with other institutions.

Pregnancy. Two patients in this series were pregnant when thrombophlebitis developed. One was in the middle of the third trimester and the other in the first trimester. Both patients were given a full course of dicumarol under our plan and reacted favorably. One was given a second prophylactic course beginning on the day of delivery and had no adverse effects. The other was delivered and followed without dicumarol prophylaxis and her progress also was good.

Post partum. Two other patients were noted to have thrombophlebitis within the first 10 days post partum and were given a course of dicumarol by our plan. In both cases progress was satisfactory. In no case was nursing of the young allowed during the mother's dicumarol treatment because of the possible deleterious effect on the infant. This is still a controversial point and so a conservative attitude was adopted by our obstetric and pediatric staffs.

These results and the observations on 2 patients who had normal menses during treatment with dicumarol (Table V) would lead us to think that the uterus is little affected by dicumarol as used here. Our observations certainly are in accord with the fine work of Barnes and his associates.

Postoperative cases. Again, the predominance not only of gastrointestinal and gynecological cases but also of fractured hips is noted in this group. The predominance of gastrointestinal cases is probably due to the disproportionate frequency of these operations here, due to the special interest of our staff in these conditions. These 38 postoperative cases represent 41.0 per cent of the entire series.

All other conditions. Of all the fractures of the lower extremity seen in our hospital during the period of this study, only 4 were treated with traction alone. None of these patients developed evidence of thrombophlebitis of the lower extremities.

The relative absence of surgery in our cases involving the hip or lower extremity would seem to indict surgery but this would be unfair. In most of our cases of fracture treatment was by internal fixation, casts, or both. Patients with fractures of the lower extremity (the majority of the hip) admitted usually a week or more after their fracture and often for secondary reparative surgery represent the great bulk of our operative fracture cases. These facts taken into due consideration would account for the figures as they stand. During the period of our study there were 60 hip operations for fracture in our hospital. In 4, or 6.6 per cent of these, thrombophlebitis developed (Table VII).

The early part of our study was contemporary with the great poliomyelitis epidemic of 1946. Seven patients with poliomyelitis

were examined for the presence of thrombophlebitis. In all the patients examined with the signs and symptoms of poliomyelitis it was easy to identify those with thrombophlebitis. Only 3 cases, however, are included in this series. In these cases the thrombophlebitis occurred in the postinflammatory state of the poliomyelitis when the signs of swelling, heat in the extremity, and elevation of vital signs should not have been caused by the poliomyelitis. Muscle pain and tenderness while present could not be used as evidence as they are common to both diseases.

That we may have missed some cases of thrombophlebitis in those seen in the acute stage of poliomyelitis and that some or all of the cases we included may have been exacerbations of poliomyelitis is not denied.

The incidence of cardiac disease as recorded is low because only those patients without other disease are included. A great number of our patients had cardiac disease along with their other difficulties but no special effort was made to correlate this finding as a separate entity.

As has been noted by Dennis, the incidence of thrombophlebitis in ulcerative colitis is about 30 per cent. In full cognizance of this fact, all patients with ulcerative colitis operated upon in our hospital for ileostomy are given prophylactic anticoagulants. As a result, none of our patients with ulcerative colitis having ileostomy operations has developed thrombophlebitis since this prophylaxis was instituted.

RESULTS

All of our results must be considered from the standpoint of our entire method of treatment which includes anticoagulants as the main instrument. Without anticoagulants the bed rest in Trendelenburg position plays a large role, in our opinion, in getting our patients well and preventing pulmonary embolism.

As has been stated, there were no cases of secondary fatal pulmonary embolism and only 2 cases of pulmonary embolism after or during supposedly adequate treatment. There was only 1 fatality in the entire group supposedly adequately treated with anticoagulants.

Following is a résumé of the average number of days before return to normal of or relief from: vital signs, 4.8 days (majority 3 to 4 days); pain, 4.0 days (majority 3 to 4 days); tenderness, 8.0 days (majority 3 to 8 days); swelling 2.0 days (majority 1 to 2 days).

Actually our 27 patients with pulmonary embolism represent 29 per cent of the entire series, a little less than the 33 per cent incidence of pulmonary embolism usually found in untreated thrombophlebitis.

CONCLUSIONS

Our observations lead us to believe that the most indicative signs in venous thrombosis of the lower extremities are swelling, tenderness, temperature change, and pain. The high incidence of deep calf tenderness in our series leads us to rely more on this sign than on the presence of tenderness to calf squeeze or a positive Homans' sign. However, we consider calf-squeeze tenderness and a positive Homans' sign as necessary adjuncts in making a diagnosis, but when present alone they are probably not as dependable as deep calf tenderness. Color changes, dilatation of superficial veins, and increase in vital signs are helpful when present but probably not of great significance in making a diagnosis of deep vein thrombosis due to the infrequency of their occurrence.

The use of anticoagulants in the treatment of our patients has been very encouraging to date and has reduced the incidence of secondary embolism from an expected 30 per cent to 2.17 per cent. It has reduced the rate of secondary fatal embolism from an expected 25 per cent to zero. The use of anticoagulant treatment has not significantly affected the over-all incidence of primary pulmonary embolism. This cannot be considered as a deficiency of the treatment because most of our patients with pulmonary embolism had already had the embolism at the time of the diagnosis of thrombophlebitis. It would seem to emphasize the value of prophylaxis.

We are impressed with the high incidence of thrombophlebitis in patients with cancer and believe that these patients should have prophylactic postoperative use of anticoagulants. Such prophylaxis seems to be indicated in patients having major gastrointestinal opera-

tions, hysterectomies, and hip fixations, especially those with cancer.

We believe the use of anticoagulants with bed rest in mild Trendelenburg position is a satisfactory way of treating thrombophlebitis. Ligations are also indicated in some cases. We do not believe sympathetic blocks necessary for the treatment of acute thrombophlebitis of the lower extremity.

For the most part, the use of dicumarol, keeping the patient's prothrombin time at 2 to 3 times normal for 14 days with the patient ambulatory for at least the last 7 days is probably an adequate course of therapy for deep vein thrombophlebitis.

It appears that the use of heparin in 50 milligram doses intravenously every 4 hours omitting the 4:00 a. m. dose may well be an adequate form of treatment. Our experience with this method is still too limited to draw any just conclusions as yet. This is also true of our small experience with heparin in Pitkin's menstruum.

It is likely that the answer to the question of thrombophlebitis does not lie in perfecting the anticoagulants and their administration, but rather in the fundamental cause of abnormal blood clotting.

SUMMARY

1. Ninety-two cases representing 105 extremities with deep thrombophlebitis of the lower extremities are presented.

2. The incidence of diagnostic signs and symptoms are recorded and evaluated.

3. A method of treatment with heparin and dicumarol used in 84 of the cases is presented.

4. The cases of 8 patients who were treated with ligation are also presented.

5. Twenty-three cases of acute iliofemoral thrombosis including 11 cases of so called phlegmasia alba dolens are presented.

6. The incidence of pulmonary embolism before and after anticoagulants is discussed.

7. The complications of anticoagulant therapy are presented and discussed.

REFERENCES

1. Allen, A.W. Bull. N. York Acad. M., 1946, 22: 1169.
2. Allen, A. W. et al. J. Am. M. Ass., 1945, 128: 397.
3. Barker et al. Surgery, 1945, 17: 207.
4. Barnes and Erwin. Surg. Gyn. Obst., 1946, 83: 528.
5. Bauer, G. Acta. chir. scand., 1940, 84: Supp. 61.
6. Idem. J. Am. M. Ass., 1946, 131: 196.
7. Birger, I. Acta. chir. scand., 1947, 95: Supp. 129.
8. Crafoord, C., and Jorpes, J. E. J. Am. M. Ass., 1941, 116: 2831.
9. Dennis, C. Minnesota M., 1948, 31: 37.
10. Edwards and Robuck. Surg. Gyn. Obst., 1947, 85: 547.
11. Frykholm, R. Surg. Gyn. Obst., 1940, 71: 307.
12. Homans, J. N. England J. M., 1941, 5: 179.
13. Hunter, et al. Surgery, 1945, 17: 178.
14. Jorpes, J. E. Ann. Int. M., 1947, 27: 361.
15. Link, K. P. The anticoagulant from spoiled sweet clover hay. Harvey Lectures, 1943–1944, 162.
16. Loewe and Hirsch. J. Am. M. Ass., 1947, 133: 1263.
17. Loewe and Richter. Surgery, 1947, 22: 746.
18. McCleery, R. S., Artz, C. D., and Sirak, H. D. Surgery, 1948. In press.
19. Miller, R. H., and Rogers, H. J. Am. M. Ass., 1929, 93: 1452.
20. Moses, W. R. N. England J. M., 1946, 9: 288.
21. Murray G., and MacKenzie, R. Am. J. Surg., 1942, 57: 414.
22. Quick, A. J. J. Am. M. Ass., 1938, 110: 1658.
23. Roessler, H. Clinical Roentgenology of Cardiovascular System. P. 161. Springfield, Ill.: C C Thomas, 1943.
24. Welch, C. E., and Faxon, H. H. J. Am. M. Ass., 1941, 117: 1502.
25. Yahr, Reich, and Eggers. Surg. Gyn. Obst., 1945, 80: 615.

THE SURGICAL MANAGEMENT OF ULCERATIVE COLITIS

G. GAVIN MILLER, M.D., F.R.C.S.(C), CHARLES B. RIPSTEIN, M.D., F.R.C.S.(C), and EDWARD J. TABAH, M.D., Montreal, Quebec

IN recent years the therapy of ulcerative colitis has undergone a radical change. Advances in preoperative preparation and in postoperative care have made surgery safer. As a result, more patients are being treated by surgical measures and more radical operative procedures are being recommended. In the past, the aim of treatment has been to put the diseased bowel at rest by diverting the fecal stream with an ileostomy. Although this form of management gives good results in some cases, it is now realized that when extensive pathological changes have occurred in the bowel wall it never reverts to normal. Continuity of the intestinal stream can seldom be restored without grave danger of recurrence. The diseased bowel may also act as a focus of infection which prevents complete restoration to health. Furthermore, the possibility of polyposis and malignant degeneration always exists. Consequently, as surgery has become safer, there has been an increasing tendency to follow initial ileostomy with resection of the colon in one or more stages (9). The results of colectomy have been relatively good. Cattell (2) states that three quarters of the patients thus treated have remained well and have been able to resume their former occupations. Others have had a similar experience. The purpose of this paper is to present the technique of surgical management which we have adopted at the Royal Victoria Hospital.

SELECTION OF CASES FOR OPERATION

Ulcerative colitis is a disease of variable severity and relatively few cases demand surgical treatment. In most clinics 20 to 25 per cent of all patients come to operation. It must be remembered that surgery is only indicated in intractable or complicated cases, and as a rule, anyone that undergoes operation represents a medical failure. For this reason, comparison of the results and mortality of medically and surgically treated groups is unfair and gives little indication of the value of any procedure.

Clinically, cases of ulcerative colitis can be divided into three groups.

Group I. The acute fulminating type with extreme toxemia, massive hemorrhage, and rapidly downhill course. The results of treatment are poorest in this group. Surgery offers little prospect of alleviation and carries a prohibitive mortality. Patients so afflicted should be treated medically with antibiotics and blood transfusion. Crohn (6) has stated that streptomycin is sometimes of value. The medical ileostomy with the Miller-Abbott tube may also be useful (11). If operation is contemplated it must be performed early before the patient is in a moribund condition.

Group II. Chronic cases of moderate severity characterized by remissions and exacerbations. Most of the surgical patients fall into this group and the indications for operation may be classified as follows:

1. *Intractable cases.* These follow a downhill course with increasingly frequent and severe exacerbations which cannot be controlled by medical therapy. Episodes of diarrhea and bleeding recur and weight loss, anemia and liver damage become more marked. In the past, such patients have been subjected to operation as a last hope. With improved preoperative preparation, and a feasible means of controlling the ileostomy, earlier surgical intervention is indicated.

2. *Complicated cases.*

a. Perforation. This complication occurs in about 1 per cent of patients. It is especially likely in acute cases or chronic cases with stricture formation. A virulent form of peritonitis results which is almost universally fatal. In most instances there are warning signs of impending perforation and these must be regarded as an urgent indication for surgery.

From the Department of Surgery, Royal Victoria Hospital and McGill University, Montreal.

b. Stricture formation. Narrowing of the bowel lumen due to scarring occurs in 5 per cent of cases of ulcerative colitis. The commonest site is in the rectum. As a rule, the stenosis is not severe enough to cause complete intestinal obstruction. The lesion is irreversible and demands surgical treatment.

c. Polyposis. This represents the most common complication in chronic cases, the incidence being 10 per cent. The lesions are pseudopolyps, representing hyperplastic islands of epithelium between the ulcerated areas. Polyposis constitutes an indication for surgery because of the danger of recurring hemorrhage and malignant degeneration.

d. Carcinoma. There has been some controversy about the frequency of malignant change in chronic ulcerative colitis. Lynn found an average incidence of 2 per cent in a large series of cases. Cattell and Boehme (4) feel that the true prevalence is greater than the reported figures. It appears likely that with more patients surviving longer periods because of improved medical therapy the incidence of carcinoma may become higher. The tumors that develop in these patients are extremely malignant and metastasize rapidly. The slightest suspicion of carcinoma demands early radical surgery.

e. Massive hemorrhage. Bleeding is fairly common during exacerbations of the disease, but massive melena is relatively rare. When it does occur, it constitutes a very serious complication and carries a high mortality. If conservative treatment does not control hemorrhage within 48 hours, surgical intervention is indicated.

f. Abscess and fistula formation. These are local complications which arise as a result of infection and ulceration in the colon or rectum. Persistent fistulas result from opening of abscesses into the surrounding tissues or neighboring organs. The only effective treatment is diversion of the fecal stream and subsequent excision of the diseased bowel. If the rectum is not removed symptoms persist despite ileostomy and colectomy.

3. Segmental ulcerative colitis (7). This represents a rare form of the disease in which the lesions are limited to an isolated segment of the colon. Such cases can be cured by resection of the involved bowel. This should be done early to avoid further extension of the pathological process.

Group III. Many patients have a very mild type of disease in which pathological changes are not severe and symptoms constitute an inconvenience rather than a disability. They rarely develop complications and the mortality is low. Such cases respond well to medical and psychiatric therapy and do not require surgical intervention unless complications or severe exacerbations ensue.

PREOPERATIVE PREPARATION

The most frequent cause of morbidity in the surgery of ulcerative colitis has been the failure to prepare these patients adequately for operation. The local lesion in the bowel is invariably accompanied by nutritional deficiencies, anemia, sepsis, and toxemia. These are usually of long duration and their correction requires an intensive preoperative regimen. The chief aims are to control symptoms, to restore nutrition, and to combat infection. In most cases the patient can be returned to excellent condition and the risk of operation is greatly reduced.

Control of symptoms. Abdominal cramps and diarrhea are usually the outstanding complaints. These can be alleviated to some extent by a bland low residue diet, absorptive powders such as bismuth and kaolin, and sedative drugs. The psychic aspect of these patients should not be neglected. It is useless to attempt psychotherapy as a primary means of treatment when severe organic changes have occurred in the bowel. However, symptomatic relief may often be obtained, and the patient can be prepared for the inevitable mental disturbance of an operation and a subsequent ileostomy.

Nutritional deficiencies. Hypoproteinemia is common in these patients due to inadequate intake, impaired absorption, and excessive loss in the bowel. It is important to realize that the plasma protein level is maintained at the expense of the tissues and a marked degree of deficiency may occur with little change in the blood. It is safe to assume that all patients with chronic ulcerative colitis are in an actual or potential state of protein deficiency. The

Fig. 1. Barium enema. Extensive ulcerative colitis involving the entire large bowel.

Fig. 2. Barium enema. Ulcerative colitis with polyposis involving the entire colon.

best form of treatment is a high protein diet. The requirements may be 200 to 300 grams a day and to reach this the diet must be supplemented by concentrated feedings. If a sufficient oral intake cannot be achieved the requirements are met by tube feedings through a nasal catheter or by the intravenous use of whole blood, concentrated plasma and protein hydrolysates. This therapy must be continued until the deficiency is fully corrected. Restoration of a positive nitrogen balance often gives rise to dramatic improvement in the patient's condition.

Vitamin deficiencies are also common. Administration of the B complex and vitamin C in adequate dosage is necessary to restore the nutritional status to normal. There is no indication that lack of any specific vitamin plays a part in the etiology or progress of the disease. The deficiencies that exist are part of the general picture of malnutrition. Liver damage of varying severity is not unusual (5). This may give rise to a prolonged prothrombin time which aggravates the bleeding tendency. Vitamin K must be administered in sufficient dosage to overcome this.

Anemia is a constant finding in severe cases, due to blood loss, malnutrition, liver damage and perhaps to toxic depression of the bone marrow. Beneficial effects have been reported from the use of liver extract, and this should be given as part of the preoperative preparation. There is no satisfactory substitute for whole blood as a means of restoring the hemoglobin to normal levels. Repeated small transfusions seem to be utilized better than occasional large ones. Blood is a good source of protein and also supplies certain nonspecific factors which appear to be of benefit in the chronically ill patient.

Because of diarrhea, the water and electrolyte balance may be disturbed. This factor must be corrected in the preoperative period by careful administration of physiological saline and glucose-saline.

Control of infection. Many papers have appeared in the literature reporting good results from the use of chemotherapeutic agents in

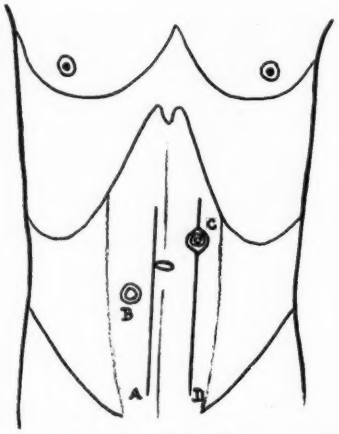


Fig. 3. Diagram of incisions used in two stage colectomy. *A*, Incision for right hemicolectomy; *B*, site of ileostomy; *C*, site of exteriorized transverse colon; *D*, incision for second stage colectomy.

ulcerative colitis. In most of these the follow-up has been inadequate and the prevalent opinion at the moment is that no antibacterial agent is of specific value in this disease (1). This has been our own experience.

From the surgical standpoint, sterilization of the bowel contents is vitally important. Even though infection may be a secondary matter it is responsible for many of the complications and deaths that result from surgical intervention. The use of sulfathalidine, streptomycin, and penicillin makes operation safer. The routine we have adopted is to give sulfathalidine for 5 to 6 days prior to operation supplemented by streptomycin orally for the last 48 hours. In the postoperative period, penicillin and streptomycin are given by intramuscular injection. With this method the bacterial count of the feces is reduced to an extremely low level, and there is often an improvement in the local manifestations of the disease. The dangers of peritonitis and wound infection are minimized in the postoperative period.

OPERATIVE PROCEDURE

It is almost always possible to plan an elective attack in a well prepared patient. In the past the surgical mortality has been high and two-thirds of the deaths have occurred in cases in which operation has been carried out as an emergency (2). Emergency operations should be avoided wherever possible.

The operation of choice has usually been an initial ileostomy which is followed in 6 months by a staged resection of the colon. We feel that a permanent ileostomy is the price which must be paid for a satisfactory result. Closure of the ileostomy leads to recurrence in a large percentage of cases.

If the fecal stream is diverted and the colon left *in situ* the patient may improve symptomatically, but the dangers of sepsis, hemorrhage and malignancy are still present. It seems to be well established that the only way to produce a lasting cure in most cases is by complete excision of the involved bowel.

It is not advisable to anastomose the ileum to the rectal stump because in the majority of patients the rectum and rectosigmoid are the most involved parts of the bowel and an abdominoperineal resection may be necessary to eradicate the disease.

Ravitch and Sabiston have advocated a pull-through type of operation in which the ileum is brought down through the intact anal sphincter resulting in a continent anal ileostomy. This procedure offers a great deal of promise but it is still too new to assess its end results.

We have adopted the policy of performing ileostomy with right hemicolectomy as an initial procedure in ulcerative colitis. The idea began accidentally when one of us (G.G.M.) was obliged to resect the right colon because of multiple perforations in a very ill patient. The result was surprising. The patient improved dramatically, her fever subsided and she began to put on weight. The resected bowel was literally "a bag of pus." It was considered that removal of the right half of the colon as an initial procedure might eradicate a source of infection and thus enable the patient to respond more quickly. This operation has subsequently been carried out in 6 patients with no deaths, and uniformly good results. We feel that it is less radical than it appears to be at first glance, and that with proper preoperative preparation it can be done with a lower mortality than simple ileostomy. The benefits are obvious. Since the right half of the colon is the absorptive part of the bowel

its removal immediately decreases toxic absorption with its consequent systemic effect. Besides removing the toxic focus of the right colon this procedure saves at least one stage in total colectomy. We also feel that such a plan of operation avoids certain complications which occur frequently with other methods. In reviewing the cases of ulcerative colitis treated at the Royal Victoria Hospital in the last 10 years we have noted the following tendencies:

1. In a large percentage of cases simple ileostomy fails to relieve symptoms and it is difficult to build the patient up sufficiently for a subsequent colectomy. Following later resection of the right colon many of these patients showed improvement.

2. Any procedure which involves anastomosis of the diseased bowel is extremely hazardous. In 6 cases in which colectomy was done with ileosigmoidostomy the mortality was 50 per cent. In all cases death was due to peritonitis.

The operation is carried out under spinal anesthesia. A long right rectus incision is made and the ileum is divided 10 to 12 centimeters from the ileocaecal valve in an area free from disease. The proximal end of the bowel is brought out through a stab wound 6 centimeters below the umbilicus and 3 centimeters to the right of the midline. This is the optimum site for the use of the Koenig-Rutzen bag (8). The terminal ileum and the right half of the colon are then removed in the usual fashion and the proximal end of the divided transverse colon is exteriorized through a stab wound. We feel that it is dangerous to attempt inversion of the diseased bowel and the stoma can be used for future irrigations and instillation of antibiotics. Silk technique is used throughout and the incision is closed without drainage with stainless steel wire.

There is usually a remarkable improvement following this procedure. Symptoms subside and weight is rapidly regained. In some cases the benefits are so marked that it is difficult to persuade the patient to undergo another operation. Excision of the remaining bowel is definitely indicated if there has been severe rectal involvement, polyposis, stricture, or anorectal fistulas. If the distal colon is not removed it should be examined periodically by proctoscopic and x-ray visualization.

The second stage is carried out in 6 months after careful preoperative preparation. Through a left rectus incision the remaining colon is resected to the level of the rectosigmoid. If the patient's condition is good and the disease involves the rectum this stage may be done as a combined abdominoperineal resection. The two team technique which we have used in cancer operations enables us to perform this in a short time with little added risk. We feel that complete colectomy is usually necessary to obtain the best results. In some cases we have shortened the interval between stages with no ill effects.

POSTOPERATIVE CARE

In the immediate postoperative period the chief aims of treatment are to prevent shock, combat infection, and replace the fluid and electrolyte loss from the ileostomy stoma. Blood transfusion, intravenous saline, and the administration of penicillin and streptomycin have solved these problems, to a great extent.

Later, the question of ileostomy care becomes important.

At the time of operation a catheter is fixed into the projecting ileum with a pursestring suture. This catheter is connected to an intermittent suction device on return to the ward. As a rule, this measure protects the skin for 48 to 72 hours and then the catheter becomes loose. Skin excoriation is difficult to prevent but with careful nursing and frequent dressings it can be kept to a minimum and has not constituted an insurmountable problem in any case. Many substances have been recommended to prevent skin digestion. Aluminum powder, kaolin, ground beef, and Lassar's paste have all been used in our series. No one has proved to be of outstanding value.

Seven to 10 days after operation an adjustable type of ileostomy bag can be used and in 2 months when the stoma has shrunk, the patient can be fitted with a made to measure Koenig-Rutzen bag. This apparatus has revolutionized the care of the ileostomy and it is now safe to say that a properly made ileostomy is no more troublesome than a colostomy. As time passes the ileal contents become more

Fig. 4. Photograph of patient, Case 1, wearing the Koenig-Rutzen bag.

solid and less irritating and the patient can lead an active life.

To date we have not attempted a pull through operation to form a continent anal stoma. If such a procedure is contemplated it would appear wise to wait 6 to 8 months until the ileostomy discharge becomes relatively solid and nonirritating.

CASE REPORTS

The following case reports illustrate some of the problems involved in the surgical management of ulcerative colitis.

CASE 1. Patient R. R., male, aged 36 years, was admitted to the Royal Victoria Hospital September 25, 1946. He had been comparatively well until 5 months before admission at which time he began to have diarrhea and slight bleeding associated with his bowel movements. The melena became more severe and he required transfusion on several occasions. There was a rapid loss of weight (40 lbs.) during the next few months.

On admission he was pale, emaciated and appeared moderately ill. Investigation by barium enema and proctoscopic examination revealed an extensive ulcerative colitis with polyposis involving the entire colon (Fig. 2).

The hemoglobin was 68 per cent and the plasma protein level was 4.28 grams per cent on admission. The protein fell to 3.63 in the next week despite a high protein diet and blood transfusion. Intensive whole blood, plasma, and amigen therapy was then commenced and the plasma protein level rose steadily to reach a height of 6.0 grams per cent at the time of the first operation (Fig. 5). On October 18, 1946 ileostomy and right hemicolectomy were performed. Extensive disease of the whole colon was found and the mesentery was thickened and edematous.

The postoperative course was complicated by obstruction of the ileostomy stoma which necessitated revision on November 7, 1946. Following this he began to gain in weight and strength and his plasma proteins continued to rise to reach a level of 7.19 grams per cent with a hemoglobin of 86 per cent. On November 20, 1946 a second stage colectomy was performed. The entire remaining colon and rectum were resected by a two team abdominoperineal procedure. During this operation a large pelvic abscess was opened contaminating the peritoneal cavity. The postoperative course was stormy being complicated by a low grade peritonitis due to Bacillus coli. This was successfully treated with streptomycin and penicillin and the patient was discharged December 18, 1946. He has remained well since that time. His ileostomy functions well and he is comfortable and active using the Koenig-Rutzen bag. He has no symptoms and his weight and general health are completely restored.

This case demonstrates several important points.

1. The state of hypoproteinemia and the massive protein intake required to overcome it.

2. The complication of low grade peritonitis which may result from perforation with local abscess or from cutting through infected mesenteric lymph nodes. This danger necessitates the use of streptomycin and penicillin in the postoperative period.

3. The short time interval between the two stages was due to the fact that carcinoma was suspected because of the pelvic mass which turned out to be an abscess.

4. The profuse ileostomy drainage in the first few postoperative days. This must be carefully measured and the fluid and electrolyte loss replaced. It has been estimated that 7 grams of sodium chloride is lost in each 1000 cubic centimeters of ileostomy drainage (Fig. 6).

CASE 2. Patient D. M., female, aged 22 years, was admitted to the Royal Victoria Hospital July 31,

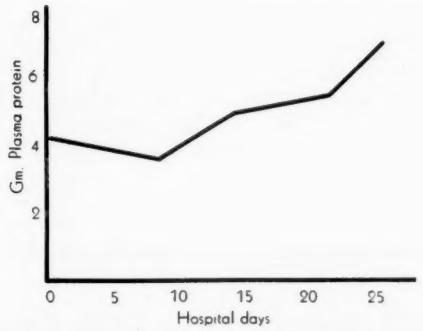


Fig. 5. Case 1. Response of plasma protein level to parenteral infusion.

Blood	750	1000	1000	1000
Plasma	500	500	1000	500
Amigen	2000	5000	3000	2000

1946. For 3 months before admission she had noticed increasing weakness and loss of weight. About 6 weeks after the onset of these symptoms she began to have severe diarrhea with blood and mucus appearing in the stool. She was admitted to hospital in her home town and treated with penicillin, sulfadiazine, and blood transfusion. This regimen did no good and she was advised to come to Montreal.

On admission the patient was pale, emaciated, and ill. Physical examination revealed no significant findings.

Barium enema and proctoscopic examination established the diagnosis of an extensive ulcerative colitis with polyposis. The disease involved the entire colon with the exception of the cecum. Culture of the stool, parasite search, and allergy investigation, all yielded negative results.

On admission her hemoglobin was 68 per cent and her plasma protein level 3.85 grams per cent.

The patient was acutely ill and ran a spiking fever of 102 to 103 degrees. She was treated with sulfathalidine, penicillin, and blood transfusions and an attempt was made to restore her nutrition. Despite these efforts her course continued downhill and on August 25, 1946 she was transferred to surgery.

She was put on intensive intravenous protein therapy with massive blood and plasma infusions. With this, her plasma proteins rose to 6.08 grams per cent and her condition improved. On September 10, 1946 under spinal anesthesia, ileostomy and right hemicolectomy were performed. The postoperative course was uneventful, whole blood transfusion, sulfadiazine, and penicillin were continued. Her condition improved rapidly and she began to gain weight. She continued to run a low grade fever and to have discharge of blood and pus per rectum. Irrigations of sulfathalidine through the colostomy opening gave some relief and she was discharged November 24, 1946, markedly improved.

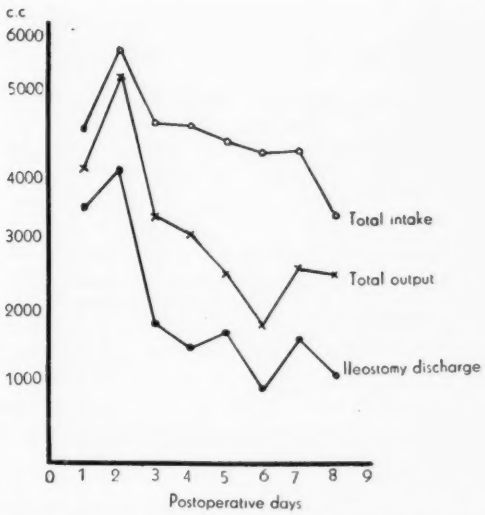


Fig. 6. Case 1. Chart of intake and output in postoperative period, illustrating ileostomy loss in the first 48 hours.

The patient was readmitted June 3, 1947. She had been well in the interval and her ileostomy was controlled with the Koenig-Rutzen bag. She had gained weight and her plasma protein level was 6.2 grams per cent. Laparotomy was undertaken June 11, 1947, after a preliminary course of sulfathalidine and streptomycin. A pelvic abscess was found and drained and the abdomen was closed. The postoperative course was uneventful and on October 7, 1947 the abdomen was again opened and second stage colectomy carried out leaving the rectum *in situ*. The postoperative course was smooth and the patient was discharged October 18, 1947. Since that time she has remained well.

This case represents the more acute fulminating type of disease. The improvement following right hemicolectomy was dramatic. The problem of restoring protein nutrition was again troublesome and large amounts of oral and parenteral protein were necessary to maintain nitrogen balance. It has been shown that these patients may lose as much as 25 grams of protein daily in the stools alone. The complication of peritoneal infection was again present and required intensive antibiotic therapy.

SUMMARY AND CONCLUSIONS

1. The indications for surgery in the treatment of ulcerative colitis are discussed. Op-

eration should be reserved for intractable or complicated cases and cases with segmental bowel involvement.

2. Preoperative preparation is important. The aims are to restore nutrition, control infection, and alleviate symptoms. Restoration of a positive nitrogen balance may be difficult and require large amounts of protein orally and parenterally.

3. The initial operative procedure of choice is an ileostomy with right hemicolectomy followed in 6 months or less by resection of the remaining diseased bowel.

4. The chief problems in the postoperative period are the control of infection which requires the use of streptomycin and penicillin, and the replacement of fluid and electrolyte loss from the ileostomy.

5. The diseased colon should be resected because of the dangers of infection, hemorrhage, and malignant degeneration. It is rarely possible to re-establish intestinal continuity without recurrence of symptoms.

6. The rectum must be removed in all cases with severe rectal ulceration, stricture, polyps, or anorectal fistulas.

7. At the present time a permanent ileostomy must be accepted as the price of a good result. With the Koenig-Rutzen bag an ileostomy does not constitute a great disability.

REFERENCES

1. Block, M., and Pollard, H. M. Gastroenterology, 1948, 10: 46.
2. Cattell, R. B. Gastroenterology, 1948, 10: 63.
3. Idem. Lahey Clin. Bull., 1944, 4: 45.
4. Cattell, R. B., and Boehme, E. J. Surg. Clin. N. America, 1946, 26: 641.
5. Comfort, M. W., Bargen, J. A., and Morlock, C. G. Med. Clin. N. America, 1938, 22: 1089.
6. Crohn, B. B. Gastroenterology, 1948, 10: 67.
7. Crohn, B. B., Garlock, J. H., and Yarnis, H. J. Am. M. Ass., 1947, 134: 334.
8. Dennis, C. Surgery, 1945, 18: 435.
9. Lahey, F. H. N. York State J. M., 1941, 41: 475.
10. Lynn, D. H. Surg. Gyn. Obst., Internat. Abstr. Surg., 1945, 81: 269.
11. Machella, M. D., and Miller, T. G. Gastroenterology, 1948, 10: 28.
12. Ravitch, M. M., and Sabiston, D. C., Jr. Surg. Gyn. Obst., 1947, 84: 1095.

CRANIOFACIAL MORPHOLOGY IN CLEFT PALATE AND CLEFT LIP DEFORMITIES

T. M. GRABER, D.D.S., M.S.D., Chicago, Illinois

MAN has a rather definite idea of just what he should look like. He is liberal enough to allow certain individual differences, but the basic physiognomical pattern is set. A man may have a withered arm or a club foot, but facial aberrations may prove a much greater handicap as the unfortunate individual tries to take his place in society. And when this critical attitude toward facial deformities is combined with the individual's own hypersensitive psychic response, the problem becomes even more complex. In congenital defects such as cleft palate and cleft lip, the surgeon starts with an abnormal pattern of obscure etiology, unknown growth and development, and questionable prognosis. Surgical management labors under a further handicap because in spite of the fact that therapy is instituted quite early, any appraisal of the results must await nature's fullest contribution conferred by maturity. Despite refinement of surgical techniques, a number of provocative questions must be answered before any definite criteria for success and failure can be established. Why do we see such wide variations in facial appearance among the cleft palate group? Are the ultimate results different for different surgical techniques and timing? Can fibrous bands of scar tissue, resulting from soft tissue repair, hold back growth and development? What is the developmental pattern in patients operated upon versus that in those not operated upon? These questions are the basis of the following report of a continuing study, in which we have attempted to determine the differences that exist between this particular congenital deformity and the normal pattern.

Embryological study reveals clearly what happens (Fig. 1). Cleft lip results from the failure of union of the maxillary and median nasal processes. According to Sicher, tenuous epithelial union does take place at one stage, but because it is not replaced with mesodermal tissue, it later gives way. Cleft palate results from a lack of fusion of the palatal processes with one another and with the nasal septum. The obscure etiology has given rise to a host of theories on the nature of cleft palate. Brophy and Logan were of the opinion that the maxilla was much broader in cleft palate patients than in normal ones and that the cleft was the result of failure of union of well developed parts (12) necessitating early ostealuranoplasty to prevent atrophy of the soft tissue and spreading of the cleft by action of the tongue and pressure of the mandible against the inclined planes of the alveoli. Others (2, 3, 4, 13, 23) have felt that there is an inherent lack of tissue and have relied on such operations as the modified Dorrance pushback techniques, attempting closure by soft tissue only. Of considerable interest to the followers of either philosophy is the timetable of maxillary growth, to serve as a basis for operative timing. Todd and Brash have both shown from large samplings of skeletal material that approximately five-sixths of the total palatal breadth have been accomplished by the end of the 4th year in normal individuals, with total width increments by the end of the 10th year (5, 28).

The present analysis of the developmental patterns and facial morphology in cleft palate is part of a serial or longitudinal survey and critical appraisal of the developing aberration. All patients are being followed and examined at regular intervals. The subjects for this investigation were 45 cleft palate patients, ranging in age from 7 months to 58 years, selected at random but with some effort to include patients not operated upon as well as those operated upon. Deformities varied from simple alveolar cleft to complete bilateral lip and palate clefts. Table I shows the varying types. The method of study was primarily roentgen-

From the Department of Orthodontics, Northwestern University, School of Dentistry.

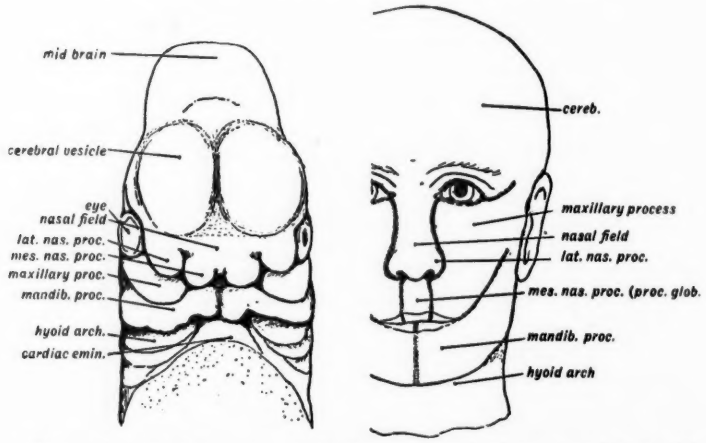


Fig. 1. Embryonal processes contributing to facial development and their adult derivatives.

ographic. The Broadbent-Bolton cephalometer (6) was used as a means of accurately positioning the patient's head to the film and x-ray tubes (Figs. 2, 3, 4). Plaster casts, photographs, and a series of five head plates were taken of each patient, and case histories were compiled. Three lateral plates, wide open mouth, physiologic rest and occlusion, and two anteroposterior plates, positions of physiologic rest and occlusion, were taken—or about 225 views in all. The following anthropometric landmarks and measurepoints seen in Figure 5 were used.

1. Nasion. The frontonasal suture, or junction of frontal and nasal bones.

2. Sella turcica. The center of the bony crypt occupied by the hypophysis cerebri. Roentgenographically a very constant profile outline seen in its lateral aspect.

TABLE I.—FREQUENCY OF TYPES OF CLEFTS

Type	Male	Female	Total	Percentage
Right unilateral lip-jaw-palate	5	3	8	17.7
Left unilateral lip-jaw-palate	13	6	19	42.2
Complete bilateral lip-jaw-palate	9	5	14	31.1
Split palate without alveolar cleft		2	2	4.4
Alveolar cleft	1		1	2.2
Split velum and soft palate	1		1	2.2

3. Porion. This is a machine registration of the center of the external auditory meatus, not necessarily corresponding to the anthropometric landmark in the skull proper, but nevertheless constant.

4. Orbitale. The lowest point on the inferior bony margin of the orbit, usually as viewed in the lateral plate.

5. Gnathion. The most outward and everted point on the profile curvature of the symphysis of the mandible.

6. Gonion. The most outward and everted point on the angle formed by the junction of the ramus and body of the mandible on its posterior inferior aspect.

7. Anterior nasal spine. The spinous process of the maxilla forming the most anterior projection of the floor of the nasal cavity.

8. Pterygomaxillary fissure. An oval looped radiolucency resulting from the fissure left by the pterygoid process of the sphenoid bone and the most posterior portion of the maxilla.

9. Pogonion. The most anterior point on the symphysis of the mandible.

10. Point A. An arbitrary [measure] point, taken at the innermost curvature from anterior nasal spine to the crest of the maxillary alveolar process, signifying the approximate juncture of the basal or supporting maxillary bone and the alveolar bone.

Since the introduction of the Broadbent-Bolton cephalometer in 1931, numerous studies have been made on growth and development of children, normal and abnormal. Of special interest are the works of Brodie and his co-workers (9, 10, 11), Broadbent (7, 8), Herzberg and Holic, Mayne, Brash, Thompson, Toothaker, Baldridge, and Downs. These, to-

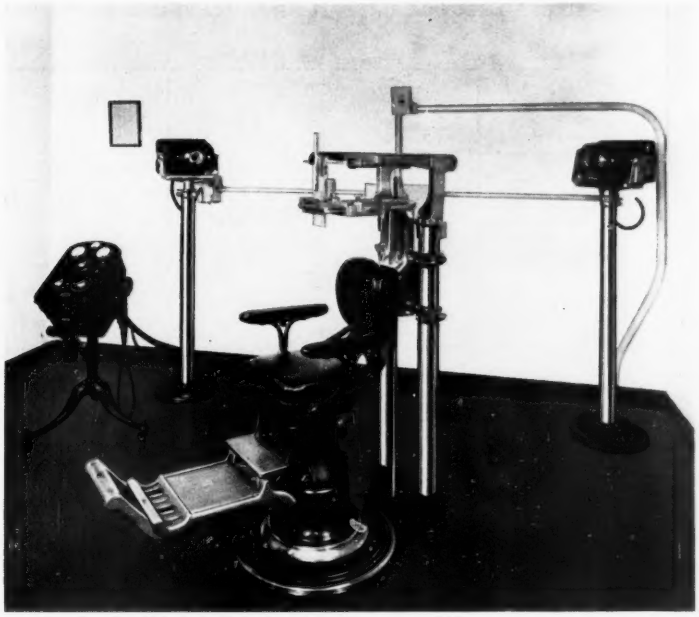


Fig. 2. Broadbent-Bolton cephalometer used for positioning patients for lateral and frontal cephalometric roentgenograms. There is a constant target-film distance of 5 feet which confers reasonably parallel rays, eliminating objectionable distortion.

gether with studies made on skeletal material (16–19, 21, 22, 29) form a basis of comparison in any study of congenital or environmental deformities. Certain criteria for determining facial characteristics have been set up, based on those used by other investigators in studies

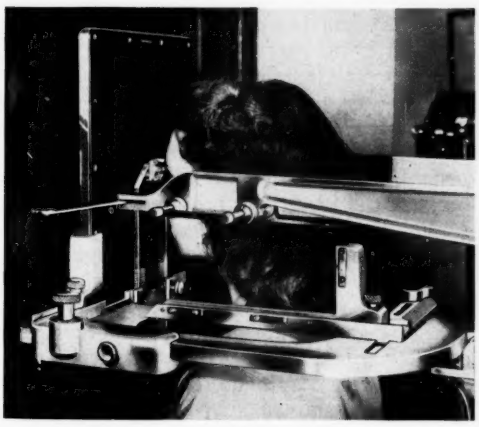


Fig. 3. Lateral view of patient in position for a frontal roentgenogram.

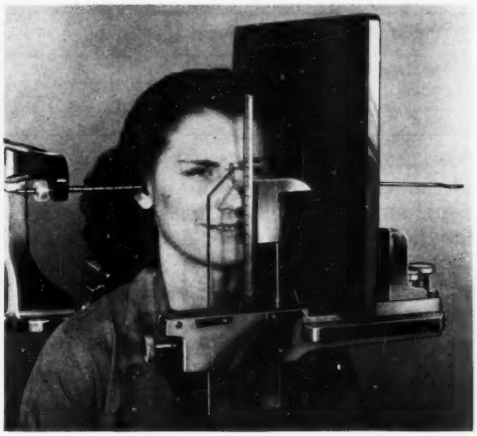


Fig. 4. Film cassette inserted for a lateral roentgenogram.

TABLE II.—NORMAL CRITERIA FOR DETERMINING CRANIOFACIAL DEVELOPMENT

Criteria	Investigator	Mean	Range	S.D.	Material
1. Nasal height	Brash	41.3% (infants)			Skulls
		42.85% (adults)			
	Brodie	43%			Normal children
	Herzberg and Holic	43.51%	14%	± 2.14°	Skulls
	Mayne	43.95%	39.7–49.5	± 2.40°	50 adults
2. Maxillary height	Mayne	41.66%	37.5–50.4	± 2.08°	50 adults
3. Intermaxillary clearance	Thompson	2–3mm			
4. Mandibular plane to Frankfort plane	Downs	21.9°	17–28°		40 adults
	Mayne	22.61°	13–36°	± 4.92°	50 adults
5. Angle of lower incisor to go-gn plane	Speidel	92.64°	78–106°	± 6.16°	
	Margolis	90°			
	Downs	91.5°	81.5–97°	± 1.5°	40 mixed
	Toothaker	94.05°	72–106°		50 adults
6. Nasion-sella-upper first molar angle	Brodie	67.59°		± 2.86°	
	Mayne	65.85°	59–75°	± 3.56	50 adults, children
	Baldridge	67.95° (Class I)		± 2.87°	
		68.46° (Class II)		± 3.15°	
		67.86° (Class II, Div. 2)			
7. Nasion-sella-gnathion angle	Mayne Baldridge	67.05°	59.5–73.5	± 3.85°	50 adults, children
		68.59° (Class I)		± 3.63°	
		70.86° (Class II)		± 3.82°	
		68.86° (Class II, Div. 2)			
8. Sella-nasion-gnathion angle	Mayne	70.99°	72.5–87°	± 3.58°	50 adults
9. Nasion-sella-gonion angle	Mayne	101.57°	95–110.5°	± 3.59°	50 adults
10. Facial angle	Downs	87.7°	82–95°		40 mixed
	Mayne	87.87°	78–94°	± 3.36°	50 adults
11. Angle of convexity	Downs	±0°	−8.5 to +10°		40 adults

of normals. Figure 5 shows the planes and landmarks used, Table II the selected normals for these criteria.

1. Face height (Nasion-gnathion). The works of Brodie, Brash, Herzberg and Holic, Thompson and Mayne have established a constant ratio of about 43 per cent for nasal height or upper face height, and 57 per cent for lower face height. This ratio seems constant from infancy and appears to be unaffected by most environmental influences. In this study, face height was further broken down into the components of the lower face—of prime concern because the insult has occurred in this area. Mayne found that maxillary height in 50 adults with normal dentitions averaged 41.66 per cent.

2. Intermaxillary clearance or freeway space. This is the amount of space between the upper and lower teeth with the mandible in physiological rest position, a remarkably constant relationship established by facial, masticatory, and skeletal musculature when the mandible is not in active function. Thompson has found

this to average 2 to 3 millimeters in the anterior region in normal occlusion. Presence or absence of teeth does not affect this position.

3. Frankfort-mandibular plane angle. The angle formed by a line tangent to the lower border of the mandible, extended posteriorly till it crosses the Frankfort horizontal plane (porion-orbitale) has been considered of significance in evaluating mandibular development, especially ramus height. In his study on normals, Downs arrived at a mean value of 21.9 degrees. Mayne used a line adjoining the anthropometric landmarks gonion and gnathion instead of a tangent and established a mean angle of 22.61 degrees.

4. Angulation of mandibular incisors. This angle has been studied by numerous investigators following the emphasis placed upon it by Tweed as a clinical criterion in orthodontic case analysis and prognosis (31). All men have found the angle to be approximately 90 degrees.

5. Nasion-sella turcica-mesiobuccal cusp of upper first molar. A rather constant angle of about 67 degrees is found in studies on normals. Specifically, any greater value would establish the molar in a posterior position, while closing of the angle means a forward positioning of the molar, or maxilla itself. In normal jaws, the upper first molar falls almost exactly on a line from the sella turcica to the anthropometric landmark gnathion—or chin point—on the mandible.

6. Facial angle. The lower internal angle formed by the juncture of the Frankfort horizontal plane with a line from nasion to pogonion (or gnathion) gives a mean value of 87.7 degrees. This measurement determines the relative position of the chin point and thus anteroposterior growth of the mandible when compared to a constant plane—Frankfort horizontal. The same information can be got from the angle sella turcica-nasion-gnathion, using the *S-N* plane as a base plane instead of the Frankfort horizontal. The angular values are different, naturally, but both are constant. The determined mean for the latter is about 80 degrees.

7. Angle of convexity (nasion-point A-pogonion). This is another means of evaluating the position of the maxilla with respect to the rest of the face and cranium. The angle formed by the lines joining these three measurepoints shows the degree of concavity or convexity of the profile. Downs found the mean value was ±0 degrees. A minus reading indicates either a deficient maxillary contribution anteroposteriorly, or an excessive mandibular accretion. It would then be necessary to examine other angular measurements of both maxilla and mandible to arrive at a differential diagnosis. A minus reading indicates a concave profile, and a plus reading indicates a convex profile.

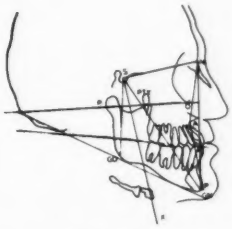


Fig. 5. Cephalometric and anthropometric landmarks and planes used in this study.

Each of the above criteria was carried through for all cases, and the mean, range, standard deviation and standard error determined. These records are on file in the Orthodontic Department of Northwestern University. For this report, a master chart has been compiled, giving the mean and range for each criterion as it compares to values arrived at in normals (Table III).

Face height was considered in order to see if there was any noticeable difference between cleft palate and normal cases. There is a broad range in upper face height, with an excessive percentage contribution of upper face height. This does not necessarily mean that nasal height is greater, but rather a lesser contribution of a component of the lower face. This seems to be the case as maxillary height is graphically deficient. All measurements here, as well as in other criteria, have been taken with the dental arches in occlusion, with one exception. That exception is the amount of intermaxillary clearance at physiologic rest. All normal studies have been made with teeth in occlusion only. However, a separate series of percentages and angular values have been determined in the cleft palate group with the

TABLE III.—CRANIOFACIAL MEASUREMENTS TAKEN WITH TEETH IN OCCLUSION

Present study			Normals		
Criteria	Mean	Range	Investigator	Mean	Range
1. Nasal height	45.3%	38–51%	Brash	41.3% (infants)	
				42.85% (adults)	
			Brodie	43.0%	
			Herzberg and Holic	43.5%	14%
			Mayne	43.95%	39.7–49.5%
2. Maxillary height	38.1%	31.9–45.4%	Mayne	41.66%	37.5–50.4%
3. Intermaxillary clearance	7.3mm	1–20mm	Thompson	2–3mm	
4. Mandibular plane to Frankfort plane—angle	24.3°	18–44°	Downs	21.9°	17–28°
			Mayne	22.61°	13–36°
5. Angle of lower incisor to go-gn plane	79.6°	65–92°	Speidel	92.64°	78–106°
			Margolis	90.0°	
			Downs	91.5°	81.5–97°
			Toothaker	94.05°	72–106°
6. Nasion-sella-upper first molar angle	74.4°	62–79.5°	Brodie	67.59°	
			Mayne	65 85°	59–75°
			Baldridge	67.95° (Class I)	
				68.46° (Class II, Div. 1)	
				67.86° (Class II, Div. 2)	
7. Nasion-sella-gnathion angle	68.9°	58–77°	Mayne	67.05°	59.5–73.5°
			Baldridge	68.59° (Class I)	
				70.86° (Class II)	
				68.86° (Class II, Div. 2)	
8. Sella-nasion-gnathion-angle	80.0°	70–95°	Mayne	79.99°	72.5–87°
9. Pterygo-maxillary fissure to line *S-X*	14mm	8–20mm			
10. Nasion-sella-gonion angle	102.4°	95–107°	Mayne	101.57°	95–110.5°
11. Facial angle	83.3°	73–99°	Downs Mayne	87.7° 87.87°	82–95° 78–94°
12. Angle of convexity	−8.2°	−30 to +9°	Downs	±0°	−8.5 to +10°

mandible at physiologic rest but must await future similar studies on normals for a means of appraisal. It is of interest to note the similarity of physiological rest values in the cleft palate group to what might be considered a valid projection from normals with teeth in occlusion and allowing a normal intermaxillary clearance (Table IV).

The difference in the length of the line nasion-gnathion in millimeters in physiological rest and occlusion headplates determined the intermaxillary clearance. A very wide range can be noted, and the mean of 7.3 millimeters is considerably more than the average values for normals. Apparently this substantiates the contention that the rest position is the result of muscular balance, that it is extremely constant, and subject to little change from birth to death. Maxillary or mandibular deficiency means a correspondingly greater in-

Fig. 6.

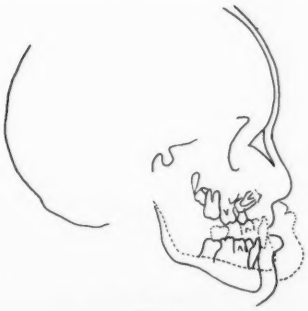


Fig. 7.

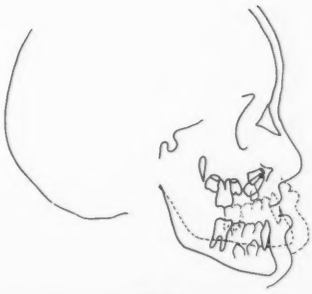


Fig. 8.

Fig. 9.

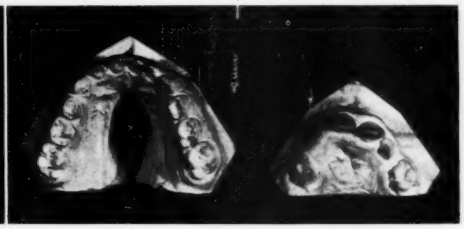


Fig. 10.

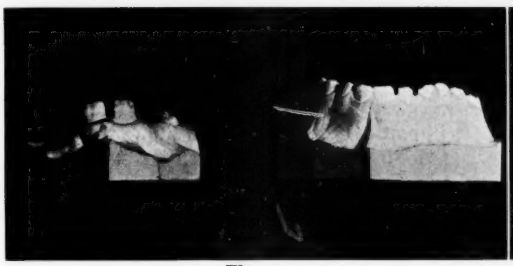


Fig. 11.

Fig. 12.

Fig. 13.

Fig. 6. Case D.Q., cleft palate, 6 years. Tracing of lateral cephalometric roentgenogram with an abnormally wide intermaxillary clearance (17 millimeters). Mandible in physiologic rest and occlusion.

Fig. 7. Case D.Q., cleft palate, 7 years. Mandible in physiologic rest and occlusion. The intermaxillary clearance has increased 2 millimeters during the past year.

Fig. 8. Case D.Q. cleft palate, 8 years. Mandible in physiologic rest and occlusion. Overclosure of the mandible, with its forward thrust of the chinpoint exaggerating the maxillary deficiency. Intermaxillary clearance, 20 millimeters.

Fig. 9. Case L.G., plaster cast on left of a patient not operated upon for complete bilateral cleft (area outlined in pencil). Model on right, Case R.P., is that of a 13 year old boy who has had 15 operations for palatal closure.

Fig. 10. Comparison of plaster cast of Case H.S., a 5 year old girl with a palate not operated upon, with that of Case R.P. of Figure 9.

Fig. 11. Frontal views of Case R.P. and Case H.S.

Fig. 12. Case R.P. Relationship of maxilla and mandible.

Fig. 13. Case H.S. Normal relation of maxillary and mandibular dental arches.

termaxillary clearance, thus requiring the mandible to overclose in order to bring the teeth into occlusion. This constancy is shown in Figures 6, 7, and 8 where, despite obvious maxillary deficiency, the musculature has attempted to maintain a normal facial balance and relation of parts. These three tracings of cephalometric roentgenograms of the same individual, taken at intervals of 1 year, show intermaxillary clearance values of 17, 19, and

TABLE IV.—CRANIOFACIAL MEASUREMENTS TAKEN AT PHYSIOLOGICAL REST COMPARED WITH NORMALS IN OCCLUSION

Present study			Normals		
Criteria	Mean	Range	Investigator	Mean	Range
1. Nasal height	44.1%	37.2–49.2%	Brash	41.3% (infants)	
				42.85% (adults)	
			Brodie	43.0%	
			Herzberg and Holic	43.5%	14%
			Mayne	43.95%	39.7–49.5%
2. Maxillary height	36.9%	30–43%	Mayne	41.66%	37.5–50.4%
3. Mandibular plane to Frankfort plane	28.8°	18.2–44.1°	Downs	21.9°	17–28°
			Mayne	22.61°	13–36°
4. Nasion-sella-gnathion angle	69.93°	60.2–78.1°	Mayne	67.05°	59.5–73.5°
			Baldridge	67.95° (Class I)	
				70.86° (Class II, Div. 1)	
				67.86° (Class II, Div. 2)	
5. Sella-nasion-gnathion angle	78.15°	70.0–93.5°	Mayne	79.99°	72.5–87°
6. Nasion-sella-gonion angle	102.7°	95–107.6°	Mayne	101.57°	95–110.5°
7. Facial angle	82.4°	70.0–98°	Downs	87.7°	82–95°
			Mayne	87.87°	78–94°
8. Angle of convexity	−6.0°	−26 to −9°	Downs	±0°	−8.5 to +10°

20 millimeters at 6, 7, and 8 years, respectively.

The value for the Frankfort-mandibular plane angle is well within the central part of the range established for normals. However, there is some suggestion of a possible tendency toward a mandibular underdevelopment. As yet there is no apparent explanation why a maxillary insult should be reflected in lack of ramus height of the mandible.

The value of 79.6 degrees for the angle formed by the lower incisor to the mandibular plane is well below the means established by any investigator on normals. Some investigators would point to an abnormally short and tight upper lip, reflected through decussating fibers of the lower lip, in constant contact with the dental units as the logical reason (15, 25). The lingual tipping of the dental units helps to adjust the normally developed pattern of the mandible to the aberrant maxillary pattern, thus reducing the apparent discrepancy.

The maxillary first molar shows a posterior positioning when compared to normal occlusions, with the angle nasion-sella-upper first molar becoming more obtuse. Further measurements involving the mandible (nasion-sella-gnathion, sella-nasion-gnathion, nasion-sella-gonion, and the facial angle) corroborate impressions gained from the Frankfort-mandibular plane figures—namely that the mandible seems normal, on the small side. The typically concave profile so often associated with cleft palate and cleft lip deformities is shown roentgenographically by a high negative angle of convexity of −8.2 degrees for the mean.

Table V is a comparison of the 8 cleft patients, not operated upon, with the 14 complete cleft patients whose lips and palates have been surgically closed. The normal mean is included to facilitate evaluation. The mean values for maxillary height (item 2) and anteroposterior development (item 11) show an

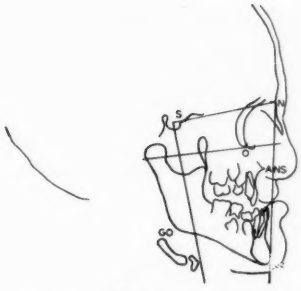


Fig. 14.

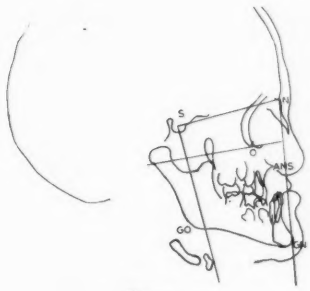


Fig. 15.

Fig. 14. Case R.P. Physiologic rest cephalometric tracing. 12 millimeter intermaxillary clearance; nasion-gnathion, 112 millimeters.

Fig. 15. Case R.P. Occlusion cephalometric tracing. Note combination of maxillary deficiency with mandibular overclosure; nasion-gnathion, 100 millimeters.

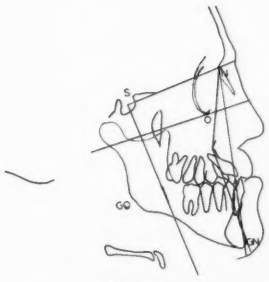


Fig. 16.

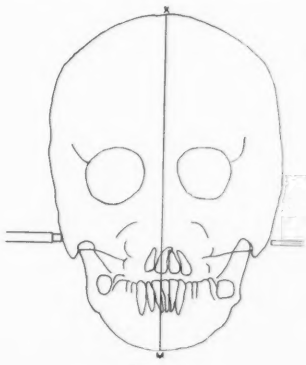


Fig. 17.

Fig. 16. Cephalometric lateral tracing of a surgically repaired bilateral complete cleft case, M.A., aged 15 years. Orthodontic treatment has been completed. Maxillary incisors have been tipped markedly forward to compensate for maxillary underdevelopment.

Fig. 17. Frontal cephalometric tracing of Case M.A., rest position.

even greater deviation from the normal in the patients operated upon than did the average of 45 cases of all types (Table III). The same measurements in the group not operated upon approach the normal means, and fall well within the normal ranges. While the intermaxillary clearance (item 3) seems to be slightly excessive in the group not operated upon—4 millimeters—this is just about half the average of 8.1 millimeters in the surgically closed complete cleft group. Lower incisor and upper first molar readings also show less deviation from the normal means in the series not operated upon as opposed to the group operated upon. Judging from measurements designed to be applied to the mandible, there still seems to be a tendency toward a slight underdevelopment in this bony unit, regardless of therapy or lack of therapy (items 4, 7, 8, 9, 10). Figure 9 shows, for comparison, the maxillary cast of a complete bilateral cleft lip and palate which had received no surgical treatment, and the cast of the same type of cleft, from a 13 year old boy who has had 15 surgical operations to provide a rock hard, functionless, flat, fibrous diaphragm that "successfully" separates the nasal and oral cavities. Figure 10 compares the cast of the latter with that of a 5 year old girl who also has had no surgical correction of the palatal cleft. Figure 11 is an

TABLE V.—MEAN COMPARISON OF RESULTS IN PATIENTS WITH COMPLETE CLEFTS OPERATED UPON AND NOT OPERATED UPON*

Criteria	Operated	Unoperated	Normals
1. Nasal height	47.1%	44.1%	43.95% (Mayne)
2. Maxillary height	37.7%	40.9%	41.66% (Mayne)
3. Intermaxillary clearance	8.1mm	4.0mm	2-3mm (Thompson)
4. Angle of mandibular to Frankfort plane	24.2°	24.4°	21.9° (Downs)
5. Angle of lower incisor to mandibular plane	78.5°	80.2°	91.5° (Downs)
6. Nasion-sella-upper first molar	75.3°	70.1°	67.59° (Brodie)
7. Nasion-sella-gnathion	69. 1°	69.0°	67.05° (Mayne)
8. Sella-nasion-gnathion	77.9°	77.7°	79.99° (Mayne)
9. Nasion-sella-gonion	102.6°	102.0°	101.57° (Mayne)
10. Facial angle	83.2°	83.6°	87.7° (Downs)
11. Angle of convexity	−9.0°	−2.6°	±0° (Downs)

*Mean values taken from cephalometric roentgenographic studies on normal groups by various investigators.

anterior view of the same casts. Figures 12 and 13 show articulated maxillary and mandibular models and emphasize the anteroposterior malrelation of the patient operated upon when compared to the one not operated upon. Figures 14 and 15 are tracings of the patient operated upon, taken at physiologic rest and occlusion, again emphasizing the vertical and anteroposterior maxillary deficiency. *The evidence afforded by these comparisons would seem convincing proof of the damaging effect which can follow operations in early life, if tissues, which should be free to expand and develop, are confined and restricted in a vise of heavy unyielding suture material and subsequent scar tissue formation.*

Nine of the present group had some degree of orthodontic therapy subsequent to surgical correction. Figures 16 and 17 show the cephalometric tracings in a patient with a result that would be considered a success clinically, if casts were the only diagnostic aid. The upper and lower incisors are in normal mesiodistal relationship, but there is a significantly high labial axial inclination of the maxillary incisors to bring them into normal interdigitation. This is combined with a large angle of profile concavity. Some observers would question the stability of this type of result where lack of basal bone support, reception of masticatory stress in an abnormal manner, and constant pressure of a hypertonic upper lip make any hope of environmental balance a dubious one. It is quite likely in many cases that the tooth to basal bone relationship is more favorable before orthodontic treatment is undertaken, and that instead of correcting malposed bony segments by moving bone itself (which can be done orthodontically), ordinary orthodontic procedures move teeth through bones to a better occlusal relationship but a more unfavorable tooth to basal bone relationship.

SUMMARY

Certain salient impressions may be gained from this initial report.

1. The maxilla in cleft palate and cleft lip patients is deficient not only in its anteroposterior and lateral growth but also in its vertical growth. There is an abnormally large contribution of upper face height to total face height when the teeth are in occlusion, due to the vertical maxillary deficiency. The high negative angle of convexity demonstrates specific lack of anteroposterior development.

2. There is a larger intermaxillary clearance or freeway space in cleft palate individuals. The variance from the normal becomes marked in complete cleft cases that have been corrected surgically. This would suggest that while there is a bony insufficiency, the general musculature, *with the exception of those involved in surgical operations*, attempts to maintain a normal developmental pattern and relation of parts.

3. Mandibular growth on the whole appears normal. Some lack of development is noted, but in any series of 45 individuals, a certain percentage will be found with similar problems. Mandibular underdevelopment is actually advantageous in some cases, reducing the disharmony resulting from a maxillary growth insult and thus improving facial balance. Mandibular overclosure, allowed by an excessive intermaxillary clearance, is a consequence of the maxillary deficiency.

4. There is an excessive lingual axial inclination of the lower incisors to the mandibular plane. It need not be called teleological reasoning to look on a hypertonic *orbicularis oris*

muscle complex as a possible explanation. Any tightness of the upper lip is reflected through decussating fibers to the lower lip, in constant contact with the dental units. The lingual positioning of the mandibular incisors reduces the underjet or the extent the maxillary incisors are abnormally posterior to the lower anterior segment, and hence should not be used as a criterion of maxillary development.

5. The maxillary first molar tends toward a posterior position with reference to craniometric measurepoints outside the maxilla.

6. We have seriously considered the propriety of early closure of cleft palates. *It is becoming apparent that surgical correction will in some instances limit the growth potential of the maxillary denture (5/6ths of which are accomplished laterally by the end of the 4th year).* In general, the greater the number of operations, the more marked the deviation from the normal. The apparently normal lateral and vertical growth in patients not operated upon where no limiting band of scar tissue is present would seem to substantiate this deduction.

7. The clinical results of orthodontic treatment, while improving the tooth relationship in many cases, do not necessarily stimulate basal bone development. Therapeutic results that are unstable have to be maintained indefinitely.

REFERENCES

1. Baldridge, J. P. Angle Orthodont., 1941, 11: 105.
2. Blair, V. P. Surg. Gyn. Obst., 1907, 4: 67–68.
3. Idem. Treatment of Cleft Palate and Hare Lip in Early Infancy. Reprint from Internat. Clin., vol. IV, series 26. Philadelphia: J. B. Lippincott Co., 1916.
4. Blair, V. P., and Ivy, R. H. Essentials of Oral Surgery. 2nd ed. St. Louis: C. V. Mosby Co., 1936.
5. Brash, J. C. The Genesis and Growth of Deformed Jaws and Palates. Pp. 67–107. London: The Dental Board of the United Kingdom, 1924.
6. Broadbent, B. Holly. Angle Orthodont., 1931, 1: 45.
7. Ibid., 1937, 7: 185.
8. Idem. Chapter in Practical Orthodontia by Dewey-Anderson. 5th ed., pp. 184–204. St. Louis: C. V. Mosby Co., 1935.
9. Brodie, Allan G. The Growth Pattern of the Human Head from the Third Month to the Eighth Year of Life. Ph.D. Thesis, Univ. of Ill., College Dent., 1940.
10. Idem. Am. J. Anat., 1941, 68: 209.
11. Idem. Angle Orthodont., 1942, 12: 109–123.
12. Brophy, Truman S. J. Am. Dent. Ass., 1927, 14: 1108.
13. Dorrance, George M. The Operative Story of Cleft Palate. Philadelphia: W. B. Saunders Co., 1933.
14. Downs, William. The normal face. Prize winning research essay presented before the American Association of Orthodontists. Columbus, Ohio, April 28, 1948.
15. Gilley, F. P. Dento-facial morphology in cleft palate. Masters Thesis, Northwestern University, School Dent., 1947.
16. Gregory, William K. Our Face from Fish to Man. New York: G. P. Putnam's Sons, 1929.
17. Hellman, Milo. Internat. J. Orthodont., 1927, 13: 475–516.
18. Ibid., 1932, 18: 777–98.
19. Idem. Dent. Cosmos, 1935, 77: 685–700, 777–87.
20. Herzberg, B. L., and Holic, Richard. Am. J. Orthodont., 1943, 29: 90–100.
21. Keith, Sir Arthur, and Campion, George. Dent. Rec., Lond., 1922.
22. Krogman, Wilton M. Am. J. Orthodont., 1939, 25: 724–31.
23. Logan, William H. G. J. Am Dent. Ass., 1927, 14: 1095.
24. Mayne, Warren R. A study of the skeletal pattern of the human face. Masters Thesis, Northwestern University School of Dentistry, 1946.
25. Merrifield, F. W. Personal communication to author, June, 1948.
26. Sicher, Harry. Chap. 1, p. 30 in Oral Histology and Embryology by Orban, B. St. Louis: C. V. Mosby Co., 1944.
27. Thompson, John R. J. Am. Dent. Ass., 1946, 33: 180.
28. Todd, T. Wingate. Am. J. Orthodont., 1930, 16: 1243.
29. Idem. Angle Orthodont., 1931, 1: 67.
30. Toothaker, James C. A study of the angle of axial inclination between teeth and their bony bases. Masters Thesis, Northwestern University School Dentistry, 1946.
31. Tweed, Charles H. Angle Orthodont., 1941, 11: 5–11.

THE STABILITY OF Ac-GLOBULIN AND OF PROTHROMBIN IN CITRATED HUMAN PLASMA

JOHN L. FAHEY, ARNOLD G. WARE, Ph.D., and WALTER H. SEEGERS, Ph.D.,
Detroit, Michigan

WITH the widespread use of stored blood, a knowledge of the stability of the various plasma components concerned in the clotting mechanism has assumed increased value. Numerous investigators have reported studies on the change in plasma prothrombin during storage, but have arrived at somewhat contradictory conclusions (1, 2, 3, 7, 8, 9, 12, 18). No reports have appeared on the stability of Ac-globulin, a plasma globulin which accelerates the change of prothrombin to thrombin. The concentration of this substance in plasma like prothrombin is less than 0.5 per cent of the total plasma proteins (15). Ac-globulin is probably the same substance as factor V described by Owren (6) which was found to be absent from the blood of a certain patient with a bleeding diathesis which was not hemophilia (4, 5). The absence of this factor from highly purified prothrombin preparations accounts for the slow rate at which these preparations are changed to thrombin even in the presence of optimum amounts of thromboplastin and calcium ions (16).

In a study of the exact role of Ac-globulin in blood clotting Ware, Murphy, and Seegers (14) came to the following conclusions: (a) Ac-globulin is inactive in circulating plasma under normal conditions. (b) At the inception of clotting Ac-globulin is first partially activated by extremely small amounts of thrombin formed from the interaction of prothrombin, thromboplastin, and calcium. (c) The presence of small amounts of active Ac-globulin then catalyzes the interaction of prothrombin, thromboplastin, and calcium. (d) The increased thrombin concentration further catalyzes the activation of Ac-globulin, and the process proceeds co-autocatalytically to complete the prothrombin activation process. The inactive form of Ac-globulin, present in the circulating plasma, is called "plasma Ac-globulin" by these investigators and the active form is called "serum Ac-globulin." In order to include Ac-globulin, the generally accepted theory of blood clotting has been modified to the following form:

$$\text{Prothrombin} + \text{Thromboplastin} \xrightarrow{Ca^{++}} \underset{\text{(Slow)}}{\text{Thrombin}}$$

$$\text{Plasma Ac-globulin} \xrightarrow{\text{Thrombin}} \text{Serum Ac-globulin}$$

$$\text{Prothrombin} + \text{Thromboplastin} \xrightarrow[\text{Serum Ac-globulin}]{Ca^{++}} \underset{\text{(Rapid)}}{\text{Thrombin}}$$

$$\text{Fibrinogen} \xrightarrow{\text{Thrombin}} \text{Fibrin(Clot)}$$

Because Ac-globulin is fundamentally concerned with the activation of prothrombin it is important to learn how the concentrations of both of these substances are changed during storage.

PROCEDURE

Blood was obtained by venipuncture from normal adult human subjects. The first few cubic centimeters were discarded in order to reduce the possibility of contamination by tissue fluids, and the experimental sample was collected in a second syringe from the same needle. Two parts of 3.2 per cent sodium citrate solution contained in the syringe was used as anticoagulant for 23 parts of whole blood, giving a final citrate concentration of 0.0087 M. After centrifugation at 2,000 revolutions per minute for 15 minutes at room temperature, the plasma was placed in a stoppered test tube in a refrigerator at 3 to 5 degrees C., and analyzed at intervals as indicated in Figures 1 and 2.

The prothrombin concentration was determined by the two stage method of analysis (11, 17) and by a modification of this method

From the Department of Physiology, Wayne University College of Medicine, and aided by a grant from the United States Public Health Service, National Institute of Health.

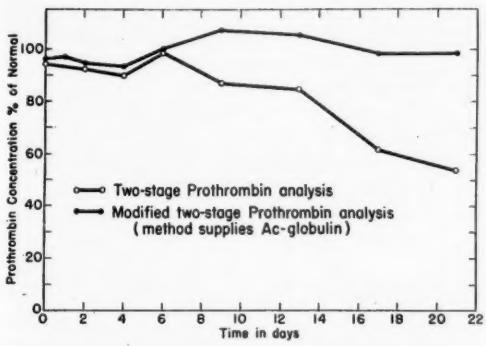


Fig. 1. Change with storage time in the prothrombin concentration of citrated human plasma as measured by two stage method of analysis and by a modification of method.

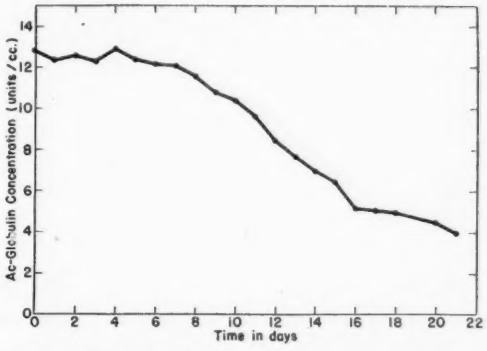


Fig. 2. Change with storage in the mean Ac-globulin concentration of 5 samples of stored citrated human plasma.

(10) in which an optimum amount of accelerator factor is especially provided in the first stage of the determination. This special maneuver of supplying Ac-globulin becomes important in the two stage analysis when prothrombin is not already associated with an abundant supply of accelerator (6, 13, 14). In the original two stage method prothrombin is activated by the action of excess thromboplastin, calcium, and any Ac-globulin which happens to be present in the analytical sample. In the modified two stage method the supply of Ac-globulin is not left to chance. It is supplied in the form of bovine serum diluted 1:600. This amount assures a quantitative change of prothrombin to thrombin (10).

The method used for the determination of Ac-globulin employs the same reagents used for prothrombin analysis. In the actual determination a standardized solution of purified prothrombin is needed. Since it does not become activated by the two stage prothrombin reagents, but does if Ac-globulin is added, the rate of thrombin formation is a quantitative measure of Ac-globulin activity. Details of the test are described by Ware and Seegers (15, 16).

RESULTS

In 6 different experiments the prothrombin level of plasma as determined by the unmodified method of analysis remained constant for a period of about 7 days, then decreased progressively to about 50 per cent of the original level at 21 days. A representative experiment is presented in Figure 1. The prothrombin level determined by the modified method remained constant for the entire period of 21 days. In 5 different experiments, mean values of which are shown on Figure 2, the plasma Ac-globulin remained constant for 7 days and then decreased to about a third of the original level after 21 days.

In several other experiments the prothrombin level was found by the modified method to remain unchanged for a period of 56 days.

In order to obtain information on whole blood a study was made of the stability of prothrombin and Ac-globulin by the same methods as previously described except that the blood was placed immediately in the refrigerator after mixing with the sodium citrate and without centrifugation. Plasma samples were removed for analysis from the supernatant plasma after the cellular elements had settled. Results similar to those obtained with citrated plasma were found for a period of 2 weeks for the stability of prothrombin in citrated whole blood. Ac-globulin was found to be somewhat less stable than in the centrifuged plasma. The decrease in activity began in less than a week. Studies with whole blood were not made beyond 2 weeks.

DISCUSSION

The apparent decrease in prothrombin level obtained with the original two stage method approximates the decrease in plasma Ac-globulin activity, and appears to be attributable

to the interference of an Ac-globulin lack in the quantitative prothrombin determination. This deficiency is corrected in the modified two stage analysis for prothrombin.

Since the 2 factors, prothrombin and Ac-globulin, were measured by methods which are considered specific and quantitative, it follows that this study does not give information as to whether other clotting factors are altered. Reports in the literature (3, 7, 8, 9) show greater changes in stored plasmas. If those changes were due to prothrombin or Ac-globulin there must have been a significant difference in the conditions of storage or the changes which those reports detected were concerned with fibrinogen or unrecognized clotting factors, or both.

Stored blood, as customarily used in hospitals, can then be considered as having full prothrombin content. A moderate diminution of Ac-globulin activity occurs on storage of blood. The nature of this decrease is such that it need not be a matter of concern in the ordinary use of the blood bank.

SUMMARY

The prothrombin content of plasma obtained from blood which contains 0.0087 M sodium citrate as anticoagulant remains constant for at least 21 days when stored at 5 degrees C. The level of Ac-globulin, under the same conditions, remains constant for a week, decreases to about 55 per cent of the initial level in 2 weeks, and to about 30 per cent in 3 weeks. The presence of formed elements has no effect on the stability of prothrombin. Ac-globulin appears to be somewhat less stable in whole blood than in centrifuged plasma.

For reliable estimation of prothrombin by the two stage method it is necessary to supply Ac-globulin if a sufficient quantity is not already associated with the prothrombin sample.

REFERENCES

1. Belk, W.P., Henry, N.W., and Rosenstein, F. Am. J. M. Sc., 1939, 198: 631.
2. Kazal, L. A., and Arnow, L. E. Arch. Biochem., 1942, 1: 169.
3. Lord, J. W., and Pastore, J. B. J. Am. M. Ass., 1939, 113: 2231.
4. Owren, P. A. Proc. Norwegian Acad. Sc., 1944.
5. Idem. Lancet, Lond., 1947, 252: 446.
6. Idem. The Coagulation of Blood, Investigations on a New Clotting Factor. Oslo: J. Chr. Gunderson Boktrykkeri, 1947.
7. Page, R. C., and de Beer, E. J. Am. J. M. Sc., 1943, 205: 257.
8. Quick, A. J. J. Am. M. Ass., 1940, 114: 1342.
9. Rhoads, J. E., and Panzer, L. M. J. Am. M. Ass., 1939, 112: 309.
10. Seegers, W. H. Josiah Macy, Jr. Conference on Blood Clotting and Allied Problems, February 1948.
11. Smith, H. P., Warner, E. D., and Brinkhous, K. M. J. Exp. M., 1937, 66: 801.
12. Ware, A. G., Guest, M. M., and Seegers, W. H. Am. J. Physiol., 1947, 150: 58.
13. Idem. J. Biol. Chem., 1947, 169: 231.
14. Ware, A. G., Murphy, R. C., and Seegers, W. H. Science, 1947, 106: 618.
15. Ware, A. G., and Seegers, W. H. J. Biol. Chem., 1948, 172: 699.
16. Ibid. In press.
17. Warner, E. D., Brinkhous, K. M., and Smith, H. P. Am. J. Physiol., 1936, 114: 667.
18. Warner, E. D., DeGowin, E. L., and Seegers, W. H. Proc. Soc. Exp. Biol., 1940, 43: 251.

PULMONARY EMBOLISM

Its Incidence, Significance, and Relation to Antecedent Vein Disease

LEO M. ZIMMERMAN, M.D., F.A.C.S., DANIEL MILLER, M.D., Chicago, Illinois and
ALFRED N. MARSHALL, M.D., Portland, Oregon

DESPITE the recent welter of literature on the subjects of thrombosis and embolism, many aspects of the problem are still clouded by confusion and doubt. Numerous prophylactic and therapeutic measures have been promulgated, the respective values of and indications for which are by no means agreed upon. Much of the data concerning this problem are based on clinical diagnoses which, unfortunately, are subject to a wide margin of error. Any factual data which bear on this subject should be of value in dispelling the vagueness and confusion which still prevail.

In search for such information, we have reviewed the pulmonary emboli observed in a large series of consecutive and unselected postmortem examinations performed over a 17 year period. Our study embraces the necropsy material of the departments of pathology of Michael Reese and Chicago Memorial Hospitals during the years 1930 to 1946 inclusive, consisting of 5,588 consecutive examinations. These two hospitals, which are served by a common department of pathology, have a total capacity of 800 beds. All cases in which pulmonary emboli were found, irrespective of their size or significance, were carefully studied from both the anatomical and clinical records. The information elicited throws light on the incidence and significance of pulmonary embolism and its relation to antecedent vein disease, and supports the indications for various prophylactic and therapeutic measures.

During the years covered in this study, there was a total of 9,980 deaths in the 2 hospitals. Autopsy was done in 5,588 of these cases, an over-all incidence of 56 per cent postmortem examinations by permission. In view of the relatively large series and the long period covered, it was our opinion that statistics drawn from the 56 per cent of the fatalities which came to autopsy could be projected with a reasonably small margin of error, to the remaining 44 per cent which did not. This projection would permit an estimate of the total number of emboli occurring in all the fatal cases. We recognize that there are two potential sources of error in such an estimate. (1) It is possible that the families might be more reluctant to give permission for autopsy following sudden and unexpected deaths, as from pulmonary embolism, and that therefore the relative incidence of major embolism might be higher in the cases not having had autopsy. We know of no way of determining the validity of this criticism, but do not believe that it introduces a serious element of error. (2) More important is the fact that deaths resulting from trauma become coroner's cases, and are not available for routine postmortem examination. This eliminates from our statistics those emboli which complicate fractures. This is a serious omission. However, despite these defects, we believe our data to be more factual than are those based on clinical diagnosis alone.

In reviewing our data, it became immediately evident that it was necessary to divide the pulmonary emboli into several categories according to their significance. They fell rather readily into three fairly distinct classes. The largest group included those small emboli with or without pulmonary infarction, which were purely incidental findings and which played no part whatever in the causation of the death of the patient. These were for the most part minute emboli, often derived from mural thrombi in the cardiac chambers in persons who died of heart disease, pneumonias, cancer, or other general causes. From the analysis of both the anatomical and the

From the Departments of Surgery and Pathology, Michael Reese and Chicago Memorial Hospitals, Chicago, Illinois.
Read before the Chicago Surgical Society, April 2, 1948.

clinical findings, it was concluded that their role was purely incidental, so far as the death of the patient was concerned, and they were included in the category designated as "incidental emboli."

A second group, intermediate in size, comprised the emboli of a larger grade, with perhaps larger infarctions, in which there was adequate explanation for the patient's death, aside from the pulmonary embolism, but in which it was conceivable that the embolus might have been a factor in weighing the balance against the possibilities of survival from a failing heart, an extensive pneumonia, a general infection or some debilitating disease. The designation "contributory emboli" has been applied to this group.

The third category were the fatal emboli, in which it was believed that the death was due directly to the embolus.

It must be obvious that in an arbitrary classification such as this, there are certain borderline cases in which there may be question as to whether a small embolus might be entirely incidental and may not have contributed in some measure to the lethal outcome. At the other end of the scale also there may be an occasional case in which it might be difficult to state that the embolus was merely a contributory and not the chief factor in the death of the patient. Nevertheless, in the overwhelming majority of cases reviewed, the differentiation into the three categories afforded no difficulty whatsoever.

The criticism will probably be raised that the exact role of the embolus in the cause of death cannot be measured with any degree of accuracy, and that, therefore, this classification of emboli is not justified. We recognize, of course, that size alone is not the only significant characteristic of the pulmonary embolus; that relatively small emboli may produce severe circulatory disturbances, and even death, by evoking spasm of the remainder of the pulmonary vessels, and possibly, by reflex vagal disturbances as described by De Takats and his associates. Also, in persons with failing circulation, it is impossible to state just how much additional embarrassment from a pulmonary embolism or infarct would be required to weigh the balance against recovery. However, it must be emphasized that we have studied the clinical as well as the autopsy records, and have considered the general condition of the patient, the nature and severity of the underlying disease, and the mode of death, in arriving at our classification. Some element of personal equation in evaluating the data cannot be eliminated. Nevertheless, we are convinced that gross error and misleading conclusions are inevitable if all emboli are lumped together, without regard to their size and to the total clinical and pathological picture, and that a division such as we have made, arbitrary though it may be, is essential if pulmonary embolism is to be placed in its proper perspective and if prophylactic and therapeutic measures are to be logically evaluated.

From a practical point of view, the cases in the first two categories are those in which, because of the gravity of the underlying disease, prophylactic ligations could not or would not have been done. In estimating the lives which might have been salvaged had this or the other measure been instituted, these could not be included. A somewhat similar division was made by Crutcher and Daniel in the material from Vanderbilt University Hospital, with results comparable to ours. In this series of 2,580 autopsies, 55 massive pulmonary emboli were found. Of these, 21 could not have recovered from their disease, even though the embolism had not occurred.

In addition to the incidence and significance of the emboli, we were greatly concerned with determining the relationship of the embolus to the antecedent vascular disease which gave rise to the embolus. It has long been recognized that vein inflammations and thromboses also fall into three fairly distinct categories, each of which carries a different degree of hazard of pulmonary embolism. In an earlier publication (6) we characterized these diseases as bland thromboses, nonsuppurative thrombophlebitides, and suppurative inflammations of the veins. Ochsner has subsequently given the name phlebothrombosis to the group of so called bland thromboses, and this designation has been generally accepted in the more recent literature. It must be recognized that the differentiation between

bland thromboses and thrombophlebitis is somewhat tenuous. Most vein inflammations are accompanied by regional thrombosis, and even the blandest thrombi provoke some degree of reactive inflammation of the adjacent vein wall. Nevertheless, vein diseases fall quite generally into the three fairly definite types.

The most severe form of vein disease is the suppurative type of thrombophlebitis. These arise within or contiguous to areas of suppuration, and the clinical picture is dominated by the manifestations of sepsis, rather than by evidences of venous obstruction. Typical examples of suppurative thrombophlebitis are seen in lateral sinus thrombosis, secondary to mastoid suppuration; in pylephlebitis from purulent appendicitis; and in the involvement of the perimetrial venous plexus in septic abortions or deliveries. Suppurative thrombi are not associated with major embolism, but showers of small emboli from the liquefaction of the thrombus may give rise to multiple small mycotic infarcts and consequent pyemic abscesses.

The intermediate form of vein disease is the nonsuppurative thrombophlebitis. This condition is best typified by the familiar puerperal "milk leg." It is usually characterized by an abrupt onset, often with chill and a rapid rise in temperature. There is very severe pain in the lower extremity and a rapidly developing generalized edema, producing the picture of the tense, white, swollen, shiny leg. With this prototype in mind, it is not difficult to differentiate the thrombophlebitic from the bland or phlebothrombotic type of venous occlusion. This last named disease has long been considered to be silent and asymptomatic. So emphatically have the younger physicians been impressed with the absence of clinical manifestations of thrombosis that, when they do encounter the disease and find manifest evidence thereof, they are inclined to question the diagnosis and suspect the existence of a thrombophlebitis.

It has long been recognized that these two vein diseases differ greatly in their tendency toward embolus formation. In thrombophlebitis the thrombus is fixed to the vein wall by an inflammatory reaction which is often of such magnitude as to produce an extensive perivascular tumefaction. Not only is the clot adherent to the vein wall but the vein itself is baked to the surrounding tissues. Such thrombi have very little tendency to break loose and form emboli. However it must be remembered that appended to the inflamed thrombus there may be a propagating, soft, red thrombus which is not firmly attached to the vessel wall and which, like any other bland thrombus, may be the source of a major pulmonary embolus. In contrast to the inflamed thrombus described, the bland thrombus lies loosely within the vein lumen and often incompletely occludes it. Such thrombi are easily dislodged and readily form the source of emboli to the pulmonary vessels.

RESULTS

As has been stated, a total of 5,588 autopsies were done in 9,980 deaths, giving an over-all postmortem percentage of 56 per cent. Pulmonary emboli of some degree were found in 345 of the 5,588 autopsies, an incidence of 6.1 per cent. It must be mentioned that ours is a general hospital population, which includes a pediatric division. Approximately 40 per cent of the autopsies in our series were in children under the age of 15, in whom the incidence of pulmonary embolism is very low. This would tend to make our percentage of total pulmonary emboli lower than it would be if only adult autopsies were included. This does not, however, affect the actual number of emboli encountered which is, of course, the important consideration.

A breakdown of these emboli according to their significance, and the type of vein disease from which they arose, follows: Of the total of 345 cases of pulmonary embolism, 166 were classed as purely incidental findings. These consisted, as has been stated, of very small emboli with or without infarction, which played no part whatever in the cause of death of the patient. Of this group, 154 emboli originated in bland thrombi and only 12 from infective phlebitides. Eleven of the latter number were of the suppurative type, and constituted numerous minute infected emboli which were part of a general pyemic picture. Only one embolus in this "incidental" group

TABLE I.—SOURCE OF PULMONARY EMBOLISM

In incidental group	
Not found	54
Heart	65
Leg veins	34
Inferior vena cava	1
Cerebral veins	1
Renal veins	1
Prostatic and ovarian veins	10
	166
In contributory group	
Not found	26
Heart	33
Leg veins	40
Inferior vena cava	7
Prostatic and ovarian veins	13
Renal veins	4
	123
In fatal group	
Not found	8
Leg veins	44
Inferior vena cava	1
Prostatic and ovarian veins	2
Renal vein	1
	56

was thought to have arisen from a nonsuppurative thrombophlebitis.

Contributory emboli, that is, emboli of a somewhat larger size, with or without infarction, which may have contributed to a degree in the death of the patient, occurred in 123 cases. Of these, 108 arose from bland thrombi; 5 from nonsuppurative thrombophlebitis; and 10 from suppurative phlebitis. In the last mentioned group, the pyemic abscesses in the lungs which were of embolic origin, were considered to have contributed toward the septic death of the patient.

Massive primary or fatal emboli were found in 56 cases in this series, an incidence of 1.0 per cent of all the autopsies. Fifty-three of these fatal emboli resulted from bland thrombi, while 3 occurred in patients with nonsuppurative thrombophlebitis, and none in instances of suppurative vein disease.

The source of the emboli, as nearly as could be determined at autopsy, is tabulated in Table I. It will be seen that in the incidental group, of those in which a source was mentioned, the most frequent site of origin was from the cardiac chambers themselves. They were thought to have broken loose from small mural thrombi in the auricular appendages in patients with cardiac decompensation or auricular fibrillation, or from the ventricular walls at the sites of myocardial infarction. The presence of such mural endocardial thrombi does not rule out, of course, the possibility of coexistent but unobserved thrombi in the veins of the lower extremities from which these small emboli may have derived their source. The leg veins were recognized as the second most frequent site of origin of the emboli in this group.

TABLE II.—DISTRIBUTION OF EMBOLI IN MEDICAL AND SURGICAL CONDITIONS

	Phlebothrombotic emboli	Thrombophlebitic emboli	Total
Incidental Medical	106	1	107
Surgical	48	11	59
Contributory Medical	72	8	80
Surgical	36	7	43
Fatal Medical	13		13
Surgical	40	3	43
Total	315	30	345

In the group of contributory emboli, while the heart was still the source of a relatively large number of emboli, the most frequent site of origin was the veins of the lower extremities. In the group of fatal emboli, almost all of the emboli arose from the veins of the lower extremities. The increasing frequency with which thrombi in the veins of the lower extremities constitute the source of embolism in the successively more serious groups of cases, is an expression of the role of size in the significance of pulmonary embolism. Large emboli must necessarily come from large vessels, and their bulk requires either great length or thick caliber. These conditions prevail particularly in the deep veins of the lower extremities. Massive emboli from other regions are extremely uncommon.

The various groups of pulmonary emboli covered in this study are further broken down in Table II, according to whether they occurred in medical or surgical conditions. It will be seen that the smallest and least important emboli occurred almost twice as frequently in patients suffering from medical conditions as compared with those with surgi-

TABLE III.—INCIDENCE OF FATAL EMBOLI AFTER OPERATION

Total number of deaths	9,980
Percentage of permission postmortem examinations	56
Total number of fatal emboli found	56
Estimated total number of fatal emboli in all cases	100
Percentage of fatal emboli found at autopsy	1.07
Number of major operations performed	152,371
Number of postoperative emboli found at autopsy	43
Estimated total number of postoperative fatal emboli	77
Incidence of fatal emboli following operation	0.0005 or 1 in 2,000

cal diseases. In the intermediate group, medical conditions still exceeded surgical ones, but the disproportion was somewhat less marked. In the group of fatal emboli the relationships were reversed, and surgical conditions exceeded medical by a ratio of 3 to 1.

In order to assay the actual hazard of pulmonary embolism in patients undergoing major surgical operations, the number of fatal emboli found at autopsy in patients who had undergone surgery was compared with the total number of operations done during the time covered by this investigation. The records show that a total of 152,371 major operations were performed during these years. In the same period, 43 fatal emboli were found at autopsy in patients who had undergone major surgical operations. It will be remembered that autopsy was done in 56 per cent of all the fatalities from all causes. Computed on this basis, it may be estimated that massive embolism was the primary cause of death in 0.05 per cent of patients undergoing major surgery, an incidence of 1 in 2,000 surgical operations (Table III).

Whether the fundamental illness which necessitates hospitalization is medical or surgical, it is usually recognized that old age, debility, and cardiac impairment are significant contributory factors in the etiology of pulmonary embolism. The age incidence in all emboli in this series, irrespective of size or significance, is recorded in Table IV. The infrequency of embolic accident in the first decades of life and the increasing incidence with advancing age, is borne out in our series. It will be noted that of the 313 cases in which the age of the patient

TABLE IV.—AGE INCIDENCE OF ALL PULMONARY EMBOLI

Years	Cases	Years	Cases
0 to 10	4	50 to 60	82
10 to 20	7	60 to 70	89
20 to 30	12	70 to 80	40
30 to 40	34	80 to 90	7
40 to 50	36	90 to 100	2

is stated, 171 (55 per cent) occurred during the two decades between 50 and 70 years of age.

The role of heart disease as a predisposing factor is stressed in most reported series of pulmonary emboli. In our study, cardiac disease, as the primary underlying disease, was recorded as follows: In the group of incidental emboli, heart disease was present in 78 of 166 cases (48 per cent); in the contributory group it was found in 45 of 123 cases (37 per cent); while in the fatal emboli it was noted in only 2 of the 56 deaths (3.5 per cent). Thus it would seem that cardiac disease is an important predisposing factor in the less severe forms of pulmonary embolism, but is of relatively minor significance in the etiology of major or fatal embolisms. However, it must be mentioned that myocardial impairment was listed as an associated anatomical finding in an additional 14 of the fatal cases. A very much closer relationship was noted in our series between fatal pulmonary embolism and malignant neoplastic disease. Of the 56 patients who died of pulmonary embolism not less than 20 were suffering from some form of malignant tumor. This confirms the role of debility and impaired general health in the predisposition to pulmonary embolism.

Seasonal and climatic variations are often listed as important predisposing factors in the etiology of pulmonary embolism. We were unable to find convincing confirmation of this impression. A breakdown of all embolic cases according to the months of the year is seen in Table V. No consistent pattern is seen.

TABLE V.—SEASONAL VARIATION OF ALL PULMONARY EMBOLISM

January	28	July	26
February	30	August	18
March	30	September	28
April	28	October	28
May	39	November	10
June	15	December	27

TABLE VI.—SUMMARY OF 56 CASES

Surgical Hosp. No. & P. Mortem No.	Age Sex Date	Clinical diagnoses	Treatment	Premonitory symptoms	Pathology at autopsy
(1) 32 M A 7 38903	44 F. March	Ovarian cyst	Oophorectomy	5th day after operation suddenly became unconscious and died 1 hour later	Thrombosis of right common iliac vein. Pulmonary embolus. Fatty infiltration of myocardium. At autopsy swelling of right leg was found
(2) 32 A 192 B 69917	70 M. Nov.	Hypertrophied prostate	Prostatectomy	2nd day after operation sudden onset of difficulty in breathing, precordial distress and nausea and cyanosis. Pulse irregular and rapid and feeble—extremis. Died 5 hours after onset	Thrombophlebitis of left common iliac vein. Emboli in intrapulmonic branches of pulmonary artery which partially obliterated artery. Thrombus in left auricular appendage. Early bronchopneumonia. Early pulmonary infarct. Arteriosclerosis
(3) 32 A 5 B 46130	48 F. Dec.	Uterine fibroids	Hysterectomy. Bilateral oophorectomy and salpingectomy Developed pneumonia postoperatively	15th day after operation, sudden attack of acute collapse, cold perspiration and gasping for breath. Pasty color, cyanotic but improved later. 19th day after operation developed similar attack as above; however, this time she died	Thrombosis left internal pudendal vein. Multiple large emboli right auricle. Older and recent riding emboli of pulmonary artery. Pulmonary infarction. Acute myocarditis with fatty infiltration. Chronic passive hyperemia. No permit to examine tibial or femoral veins
(4) 32 A 234 B 56838	44 F. Nov.	Fibrosis of uterus	Hysterectomy	7th day after operation, uneventful convalescence and allowed to walk. 8th day after operation, patient walked to bathroom this morning and while at stool suddenly collapsed. Became cyanotic, gasped for breath and died in 5 minutes	Thrombosis of left posterior tibial vein. Massive riding pulmonary embolus. Recent infarct, left lower lobe. Embolus in right auricle. Left leg is larger than right.
(5) 32 A 121 B 50623	40 M. May	Street accident—bruises and strains of left ankle	Bed rest	Pain right chest 3 days. 4th hospital day, sudden onset of dyspnea, cyanosis, fast pulse, fall in blood pressure, struggled violently for breath, and died one hour later	Old laceration of left lower leg. Thrombosis of left femoral vein. Riding embolus in right ventricle extending into pulmonary artery. Multiple emboli in smaller branches of pulmonary artery. Infarctions of lung
(6) 33 A 59 B 6187	40 M. Mar.	Carcinoma of stomach	Cecostomy	3rd day after operation, pain on breathing left lower chest. 4th day after operation cyanosis, poor pulse. Sudden onset of restlessness, gasping for breath, clutching at throat, marked cyanosis, cold, clammy and patient died in 25 minutes.	Carcinoma of stomach with perforation. Peritonitis. Thrombosis right femoral vein. Pulmonary embolism. Both legs edematous, especially the right.
(7) 33 A 203 B 68956	60 F. Nov.	Carcinoma of the ovary	Right salpingo-oophrectomy. Good postoperative course	12th day after operation sat up in chair. Patient had sudden attack of air hunger, pulse became poor and feeble, cold sweat, ashen hue, cyanosis, coma. Died 45 minutes after onset of attack	Thrombosis of left femoral artery. Riding embolus both branches of pulmonary artery. Slight pitting edema of legs
(8) 35 M A 13 48074	51 M.	Strangulated right femoral hernia	Operated upon and reduced	4th day after operation complained of faintness and died in 7 minutes while on bed pan	Recent surgical incision. Varicosties of superficial veins of lower extremities. Thrombosis of left femoral vein. Pulmonary embolus—massive chronic passive hyperemia of lungs. Acute pyelitis. Early hemorrhagic infarction of lungs. Fatty myocardium.
(9) 35 M A 3	62 F. Jan.	Marked obesity. Ovarian cyst	Removal of ovarian cyst. Good recovery	9th day after operation complained of severe pain over left lower lung area and marked friction sounds were heard anteriorly. 10th day after operation labored, painful breathing, face cyanotic. 19th day after operation sudden attack of cyanosis, air hunger, imperceptible pulse, and died in 5 minutes.	Recent surgical incision. Bilateral pulmonary emboli. Multiple infarcts of left lower lung. Emphysema. Fatty infiltration of right ventricle. Passive congestion. No source of emboli could be found even though thorough search was carried out

TABLE VI.—SUMMARY OF 56 CASES—Continued

Surgical Hosp. No. & P. Mortem No.	Age Sex Date	Clinical diagnoses	Treatment	Premonitory symptoms	Pathology at autopsy
(10) 36 A 310 C 17084	53 F. Dec.	Fibroids of uterus	Hysterectomy	Uneventful postoperative course until 10th day after operation sudden onset of patient becoming cold and clammy, pulseless, no blood pressure. Heart tones poor and irregular. Died 1 hour, 16 minutes after onset.	Thrombosis left iliac vein. Massive embolus of main pulmonary artery
(11) 36 A 163 C 7133	45 F. May	Cholelithiasis	Cholecystectomy	7th day after operation out of bed. 8th day after operation out of bed, suddenly felt faint, pulseless, cyanotic, cold and clammy. Died 15 hours later	Massive pulmonary emboli. No edema of legs. Varicose vein and ulcers
(12) 37 A 64 C 19987	65 M. Feb.	Mesenteric thrombosis	Bowel resection. 9th day after operation patient had secondary closure. Also developed wound infection and pneumonia during postoperative course	Left leg noted to be swollen on 20th day after operation. Also on 20th day after operation patient suddenly began to perspire, gasped for breath, and became cyanotic and died in 25 minutes	Generalized arteriosclerosis. Thrombosis superior mesenteric artery. Thrombosis left femoral vein. Massive pulmonary embolus. Marked coronary sclerosis. Healed infarct. Recent and organizing bronchopneumonia
(13) 37 A 86 C 21185	30 M. Mar.	Fracture left femur	Closed reduction and immobilization in cast	On 12th day after operation patient was found dead. Had been talking to other patients 10 minutes earlier	Fracture left femur. Thrombosis femoral vein. Massive pulmonary embolus. No edema of legs
(14) 37 A 264	41 F. Oct.	Acute cholecystitis	Cholecystectomy	20th day after operation while on bed pan expelling enema, patient suddenly became dyspneic, broke out in cold sweat, became cyanotic and died.	Recent embolus, pulmonary artery with complete occlusion of right and left pulmonary arteries. Multiple small pulmonary emboli in left upper lobe. Recent infarct in base left lower lobe. Recent thrombosis left femoral vein and right internal iliac vein
(15) 37 A 78 C 20764	75 M. Mar.	Incarcerated direct left inguinal hernia	Herniorrhaphy	8th day after operation helped into wheel chair; complained of dizziness, pulse became weak and patient became cyanotic. Died 4 hours later	Massive pulmonary embolus. No edema of legs noted
(16) 37 A 270 C 32758	62 F. Oct.	Carcinoma of the ovary	Exploratory laparotomy	5th day after operation patient had sudden attack of dyspnea, became cold, pulseless and cyanotic, and died 15 minutes later	Thrombosis of deep veins of left lower leg. Massive pulmonary embolus. Edema of both legs
(17) 38319 C 49691	38 F. Oct.	Fibroids of uterus	Hysterectomy	10th day after operation while walking became weak and dizzy, pulseless, dyspneic and died 14 hours after onset	Thrombosis right femoral vein. Embolus in main branch of right pulmonary artery. Embolus in left pulmonary artery. Right thigh larger than left.
(18) 38 A 277 C 47160	51 M. Sept.	Diabetic gangrene and cellulitis	Left thigh amputation	20th day after operation sudden onset of cyanosis and dyspnea while talking to wife, and fell back dead	Secondary suppuration of wound of left thigh. Thrombosis right posterior tibial vein. Massive pulmonary embolus. Generalized arteriosclerosis.
(19) 38 A 254 C 45904	62 F. Sept.	Carcinoma of duodenum	Gastroenterostomy. Diffuse peritonitis upper abdomen. Stormy postoperative course.	55th day after operation up in chair and when returning to bed suddenly seized with severe pain, nausea and dyspnea. Died in 15 minutes	Adenoma of duodenum. Peritonitis. Thrombosis left renal vein. Pulmonary embolus. Pulmonary infarct
(20) 38 M A 32 61251	37 F. Nov.	Pregnancy	Cesarean section. 8th day postoperative wound disrupted and was resutured	9th day after operation patient apprehensive. 11th day after operation slight cyanosis, tachycardia, dyspnea. 12th day after operation while on bed pan, patient suddenly went into shock. Blood pressure dropped to 80/20. Pulse weak and irregular and while being prepared for embolectomy, she died. Attack lasted 1 hour	Recent well healed incision. Edema of right lower extemity. Pulmonary embolus—main branch of pulmonary artery. Splenic hyperplasia
(21) 38 A 98 C 40240	60 M. Apr.	Carcinoma of sigmoid with perforation	Cecostomy and drainag	8th day after operation pains in left lower chest. 12th day after operation friction rub—infarct? Pulse suddenly became imperceptible and patient died.	Massive pulmonary embolus. Thrombosis deep veins right leg. Bronchopneumonia

TABLE VI.—SUMMARY OF 56 CASES—Continued

Surgical Hosp. No. & P. Mortem No.	Age Sex Date	Clinical diagnoses	Treatment	Premonitory symptoms	Pathology at autopsy
(22) 38 A 6 C 35442	63 F. Dec.	Fracture of hip	Closed reduction and cast	4th day after operation syncope and fibrillation. 5th day after operation dyspnea and gasping for breath. 22nd day after operation sudden onset of dyspnea, cyanosis, cold and clammy. Pulse weak, rapid and thready. Died in 20 minutes.	Fracture neck left femur. Organizing thrombus in left femoral vein and retrograde thrombus in left popliteal and tibial vein. Recent thrombus in right popliteal and tibial vein. Recent massive embolus in main branch pulmonary arteries. Multiple infarcts of lungs
(23) 39 A 55 C 55367	59 M. Feb.	Benign prostatic hypertrophy	Transurethral resection	On 1st day after operation patient had pains over left kidney area. 4th day after operation chilliness around knees and ankles. 5th day after operation patient suddenly had epigastric and substernal pain and marked difficulty in breathing after urinating and died 5 minutes later, though he was given oxygen and artificial respiration	Massive pulmonary embolus (right and left primary branches). Thrombosis of prostatic plexus of veins. Fatty infiltration of right ventricle
(24) 39 M A 13 C 62528	50 F. Apr.	Carcinoma of cervix of uterus	Exploratory laparotomy. Radium insertion	Patient was explored and found to have carcinoma of the uterus, which was fixed to the bladder. 15 days later radium was instituted and 12 hours later patient became dyspneic, blood pressure dropped and patient died 8 hours later.	Squamous cell carcinoma of cervix uteri. Phlebothrombosis of left posterior tibial vein. Embolus of main branch of pulmonary artery. Marked arteriosclerosis. Recent myocardial infarction
(25) 39 A 133 C 58497	55 F. May	Intestinal obstruction	Exploratory laparotomy and cecostomy	Elevated pulse rate on 18th day after operation 22nd day after operation had pains in right shoulder. 23rd day after operation the patient became pulseless, blood pressure dropped to 96/84 and patient went downhill and died rapidly	Pulmonary embolus. Phlebothrombosis right iliac vein. Papilliferous fibrocystadenocarcinoma of the ovary (bilateral) with metastases to visceral and parietal peritoneum, mesentery, diaphragm, and wall of left chest
(26) 39 A 180 C 62940	26 F. Aug.	Pulmonary tuberculosis	2d stage thoracoplasty at which time ribs VI through XI were removed	3rd day after operation patient became cyanotic, respirations increased, pulse increased, blood pressure dropped to 100 and patient died in one hour.	Massive pulmonary embolus. Tuberculous bronchitis. Caseous tuberculosis of left lung. Fibrinous pleuritis. Miliary tuberculosis of the liver
(27) 39 A 189 C 63729	94 F. Aug.	Carcinoma of left breast	Simple mastectomy	Well until 8th day after operation, at which time skin became cold. Lips and nails became cyanotic. Pulse feeble and thready. Heart rate irregular and patient died within 10 minutes. Patient had been up since 3rd day after operation. On 2nd day after operation a shackle had been placed on right leg because patient was unco-operative	Pulmonary embolus in main right pulmonary artery. Phlebothrombosis of right posterior tibial artery. Early bilateral confluent bronchopneumonia. Fibrosis and fatty infiltration of myocardium
(28) 39 A 203 C 59400	73 F. Sept.	Carcinoma of the rectum	Cecostomy	Patient went progressively downhill after surgery and was in bed most of time. Developed cardiac decompensation and died 3 months later	Phlebothrombosis of both iliac veins and inferior vena cava. Massive pulmonary embolus occluding left subdivision of pulmonary artery. Adenocarcinoma of rectum
(29) 39 A 258 C 66766	69 M. Nov.	Benign prostatic hypertrophy	Suprapubic cystotomy	5 days after operation had severe abdominal and back pain. 10 days after operation had severe pains in left chest while in bed, with rapid pulse. 11th day after operation had severe precordial pain. 27th day after operation had a swollen, painful, edematous warm left leg. 30th day after operation pulse elevated. 33th day after operation patient suddenly died	Thrombophlebitis left femoral vein. Multiple large riding emboli of pulmonary arteries. Old thrombi smaller pulmonary arteries. Hemorrhagic infarcts of lungs, both bases. Myocardial fibrosis

TABLE VI.—SUMMARY OF 56 CASES—Continued

Surgical Hosp. No. & P. Mortem No.	Age Sex Date	Clinical diagnoses	Treatment	Premonitory symptoms	Pathology at autopsy
(30) 40 A 44 C 73167	56 F. Nov.	Acute cholecystitis	Cholecystectomy and appendectomy	Patient ran atypical course with weak pulse, temperature of 101° to 102° and 104°. Dyspnea, and no cyanosis. 8th day after operation patient was improved. 12th day after operation patient suddenly became cyanotic and dyspneic, pulse became rapid and weak and patient died within a few minutes.	Localized peritonitis at hilus and organized peritonitis in fossa of gall bladder. Hemorrhage over anterior surface of liver, over posterior and lateral surface of cecum. Phlebothrombosis left posterior tibial vein. Large embolus left pulmonary artery.
(31) 40 M A 18 C 66014	72 F. Apr.	Diabetes Cellulitis right leg	Symptomatic treatment	While in hospital had a "stitching" pain across the lower chest and could not breathe. 7 days later patient was discharged from the hospital, and while on the way home in the taxi, patient suddenly became short of breath, cold, cyanotic and died in 40 minutes. At autopsy left calf found to be larger than right leg.	Phlebothrombosis of left posterior tibial veins. Multiple pulmonary emboli, old and recent. Pulmonary hemorrhage right lower lobe. Generalized arteriosclerosis. Minute foci of bronchopneumonia
(32) 41 M A 14 C 69428	41 M. Mar.	Hernia	Hernia repair	Patient had bilateral hernia repair. Developed sharp pains in chest; made worse by coughing. Also had elevated pulse. During following weeks patient had episode of chest pain, fever, blood-tinged sputum, pleural friction rub, dyspnea and tachypnea. 19th day after operation swelling of entire left leg noted and saphenous vein was palpated and a red streak was present in left thigh. 60th day after operation patient suddenly died with attack of dyspnea, tachypnea, cyanosis, shock and weak irregular pulse	Recent organizing and canalized thrombi in left common iliac, external iliac femoral and saphenous veins and deep venae comites. Multiple bilateral recent and organized pulmonary emboli. Recent and organized pulmonary infarcts of lower lobes. Organizing pleuritis lower left lobe. Swelling of entire left leg
(33) 41 A 73 C 91562	45 F. Mar.	Intestinal obstruction	Exploratory laparotomy and at surgery a large ovarian cyst was found attached to the descending colon which could not all be removed. Patient went into shock after surgery and developed peritonitis. Became distended and a cecostomy was done	5 days after cecostomy suddenly became dyspneic and cyanotic and died in a few minutes	Propagating embolus of main pulmonary artery. Swelling of both legs. Veins of pelvis thrombosed. Adenocarcinoma of descending colon with marked narrowing of lumen. Acute fibrinopurulent peritonitis. Pyelonephritic and arteriosclerotic scars of kidneys
(34) 41 M A 9 69422	64 M. Feb.	Cataract of left eye	Surgery for cataract of left eye	Postoperative course uneventful until 4th day. Temperature went to 102°. 6th day after operation patient felt dizzy and became cold, clammy, perspired profusely. Pulse became rapid, weak and blood pressure fell. 7th day after operation another attack occurred with slight cyanosis. 8th day after operation temperature rose, and from then on started down. 20th day after operation patient became cyanotic, cold, clammy, rapid pulse and weak and died shortly thereafter. Patient also coughed up blood-tinged mucus prior to death. At autopsy left leg found to be larger than right leg.	Phlebothrombosis of left hypogastric vein. Multiple massive pulmonary emboli. Pulmonary infarction right lower lobe. Acute fibrinous pleuritis. Atelectasis of left lower lobe. Arteriosclerosis
(35) 41 A 82 C 01691	67 F. Apr.	Carcinoma at junction of descending and sigmoid colon	Transverse colostomy	4th day after operation sudden onset of tachycardia to 140, tachypnea to 36. Precordial pain, dyspnea, cyanosis, slight cough and apprehension. 7 days later, patient had a sudden attack of dyspnea, shallow respiration, cold clammy skin and death in an hour	Phlebothrombosis of left popliteal vein. Multiple pulmonary emboli. Primary adenocarcinoma of uterus. Hemorrhages with early infarcts of both lower lobes of lungs. Focal fatty degeneration of myocardium and myocardial fibrosis

TABLE VI.—SUMMARY OF 56 CASES—Continued

Surgical Hosp. No. & P. Mortem No.	Age Sex Date	Clinical diagnoses	Treatment	Premonitory symptoms	Pathology at autopsy
(36) 41 A 213 C 99317	53 F. Aug.	Carcinoma of colon	Incision and drainage over left costo-vertebral region	Developed hemoptysis, night sweats and elevated pulse. 8 days after incision and drainage, patient went into shock and died quickly. At autopsy table it was first noticed that right leg was swollen	Phlebothrombosis of veins of right calf muscle. Massive pulmonary emboli. Recent hemorrhagic infarct right lower lobe. Primary fungating, polypoid ulcerating carcinoma of sigmoid colon with extension to serosa. Abscess left kidney with rupture into left perinephritic space.
(37) 42 A 21 D 4922	56 M. Jan.	Benign prostatic hypertrophy	Prostatectomy	28th day after operation developed a slight cough. 29th day after operation felt dizzy when he sat up. 31st day after operation he was found dead while sitting on toilet. At postmortem examination the left leg was found to be 5 cm. greater in circumference than right leg. Nurses notes: 12th day after operation revealed pains in left calf. 22nd day she noted left foot to be blue and edematous	Phlebothrombosis of left common iliac and popliteal veins. Multiple emboli to smaller branches of pulmonary artery in right lower lobe. Massive recent embolus to right and left branches of pulmonary artery. Recent infarct of right lower lobe with fibrinous pleuritis. Generalized arteriosclerosis.
(38) 42 A 271 D 19413	58 M. Oct.	Right suprarenal cyst	Surgical removal of right suprarenal cyst	10th day after operation, developed pains in right calf. Thrombophlebitis diagnosed and treated with x-ray and immobilization. Temperature persisted, had chills and swelling persisted. 20th day after operation, sudden severe dyspnea with pallor. Given papavarine, atropine, intracardiac adrenalin, coramine and oxygen. Stopped breathing in 5 minutes. Heart stopped several minutes later	Thrombosis of right iliac and femoral veins. Massive pulmonary embolus. Absence of right suprarenal cyst. Myocardial fibrosis. Multiple polyps of rectum
(39) 43 A 88 D 28963	59 F. May	Vesicovaginal fistula and carcinoma of cervix.	Transplantation of both ureters	12th day after operation patient had sudden onset of severe dyspnea, cyanosis, ashen color, peripheral vasomotor collapse and sudden death. At autopsy table, it was found that circumference of left leg was larger than right	Phlebothrombosis of deep veins of left leg. Massive pulmonary embolus in right ventricle pulmonary artery and its branches. Necrosis at site of anastomosis of right ureter and sigmoid colon with separation of ureter. Severe bilateral ureteropyelitis. Acute suppurative pyelonephritis of right kidney. Extension of carcinoma into parametrial tissues and metastases to ovaries
(40) 43 A 90 D 30325	60 F. May	Carcinoma of cervix	Biopsy of cervix and insertion of radium	Patient complained a lot of packing at end of 1st day after operation. 2nd day, suddenly expired after a few gasping respirations. Right leg found to be larger than left at autopsy	Pulmonary embolus. Primary ulcerating adenocarcinoma of uterus. Pyometra. Metastases to peritoneum, peritoneal and retroperitoneal and inguinal lymph nodes
(41) 43 A 153 D 33650	46 F. July	Fibroids of uterus	Hysterectomy. During surgery blood pressure fell from 200/120 to 90/60	Had normal convalescence until 7th day after operation when patient suddenly became moribund after returning to bed from wheel chair —this being the 2nd day of such activity, and died quickly after this	Massive embolus in right auricle, ventricle and pulmonary artery. Pulmonary edema. Generalized arteriosclerosis. Meckel's diverticulum. Right leg larger than left noted at autopsy
(42) 43 A 170 D 33712	57 M. Aug.	Hernia repair. Benign prostatic hypertrophy	Transurethral done after hernia repair because of urinary difficulties. Had to be resected again 3 days later because of continued urinary difficulties	Patient found on bathroom floor gasping for breath and died shortly thereafter on 3rd day after operation after last transurethral operation	Saddle embolus of pulmonary artery extending back into right ventricle and auricle. Adherent embolus of pulmonary artery branch in right lower lobe of lung. Bronchopneumonia. Early myocarditis. Fatty infiltration of myocardium

TABLE VI.—SUMMARY OF 56 CASES—Continued

Surgical Hosp. No. & P. Mortem No.	Age Sex Date	Clinical diagnoses	Treatment	Premonitory symptoms	Pathology at autopsy
(43) 45 A 42 D 59656	55 F. Feb.	Carcinoma of cecum	Resection of carcinoma and primary anastomosis	Patient went into shock following surgery. 3rd day after operation sutures were removed and patient developed a coughing spell and wound disrupted and had to be closed. 6th day after operation patient suddenly became cold and clammy with rapid respirations and died shortly thereafter.	Phlebothrombosis of right common iliac vein. Papilliferous adenocarcinoma of the cecum. Large pulmonary embolus lodged at trunk of pulmonary artery. Multiple small emboli of lungs. Marked passive hyperemia of abdominal viscera. Thrombosis of branch of portal vein. Multiple myofibroma of uterus. Metastatic nodules in the liver.
Medical Hosp. No. & P. Mortem No.	**Age Sex Date**	**Clinical Diagnoses**	**Treatment**	**Premonitory Symptoms**	**Pathology at Autopsy**
(44) 31 A 182	67 M. Sept.	Prostatic hypertrophy	Medical	After admission, had what appeared to be a typical attack of coronary occlusion. 4th day after admission, sat on commode to pass urine, no success, and returned to bed, was sitting up, suddenly head fell forward, became weak, cold clammy sweat, pulseless and died	Early organizing thrombus of right femoral and iliac veins. Massive riding embolus of both pulmonary arteries. Hypertrophy and dilation of heart. No external evidence of edema of legs seen
(45) 32 A 161 B 56964	64 M. June	Carcinoma of pancreas; diagnosed at exploration 4 months previous	Medical	26 days after admission, patient was found dead while sitting on toilet	Thrombosis of common iliac veins. Massive pulmonary embolus. Edema of both lower legs
(46) 35 A 28 B 86961	47 M. Feb.	Partial bowel obstruction	Medical	Found on floor of bathroom by nurse, semiconscious, rapid shallow respiration, pallor, pulse of 110, no blood pressure, and died one hour later	Lymphosarcoma of stomach. Thrombosis left femoral vein. Bilateral pulmonary embolus. The left thigh is slightly larger in circumference than the right
(47) 36 A 35 C 2250	77 M. Feb.	Arteriosclerosis	Medical	20th day patient went to washroom and on returning complained of epigastric pain; developed tachycardia, became cyanotic and died in 40 minutes	Thrombosis right posterior tibial vein. Multiple pulmonary emboli. Right leg slightly larger than left
(48) 38 A 132	38 M. May	Tabes dorsalis arthropathy. Cord bladder	Medical	While receiving enema became cyanotic, breathing labored, pulse imperceptible, died in 1 hour	Tabes dorsalis. Acute suppurative arthritis left knee. Thrombosis of veins of calf of left leg Massive pulmonary embolus.
(49) 39 A 198 C 64722	53 F. Sept.	Hypertension and precordial distress	Bed rest at home 5 weeks prior to entry into hosp.	Had pains in left leg. Also had varicosities and surrounding redness of left leg and induration and heat	Old and recent thrombosis of superficial veins of left lower leg. Massive pulmonary embolus (left and right subdivisions of the pulmonary artery) and multiple emboli to radicles of botn divisions of pulmonary artery. Multiple pulmonary infarcts. Mural thrombus right ventricle. Myocardial fibrosis
(50) 41 A 121 C 94016	62 F. May	Carcinoma of uterus	In hospital for observation. Had a 2–5 year history of vaginal bleeding. Dyspnea, orthopnea, cough, ankle edema, hemoptysis	While attempting a portable x-ray of abdomen, patient screamed, gasped, and died suddenly	Primary polymorphous sarcoma of uterus. Phlebothrombosis of right tibial vein. Recent and old embolism to both pulmonary arteries. Hypertrophy and dilatation of heart
(51) 41 A 252 D 1521	43 M. Oct.	Carcinomatosis	Symptomatic	Pains right lateral thigh 1 week. Severe epigastric pain. Blood pressure fell. Pulse rate increased and patient became cyanotic, cold and died suddenly.	Phlebothrombosis of popliteal and calf veins right leg. Massive pulmonary embolus. Lymphosarcoma involving retroperitoneal, mediastinal, peritoneal and infraclavicular nodes with extension to pancreas, gastrointestinal tract, omentum and peritoneum.

TABLE VI.—SUMMARY OF 56 CASES—Continued

Medical Hosp. No. & P. Mortem No.	Age Sex Date	Clinical diagnoses	Treatment	Premonitory symptoms	Pathology at autopsy
(52) 42 A 79 D 8507	25 M. Mar.	Chronic bronchitis and pleuritis	Symptomatic	One week after admission, because of chest pains, he had sudden onset of severe cyanosis, dyspnea, and weak pulse, and he died in 30 minutes, though oxygen and stimulants had no effect	Massive pulmonary emboli with complete occlusion of major pulmonary artery and its branches. Relatively recent pulmonary emboli with hemorrhagic infarctions of left upper lobe and right lower lobe. Mild chronic bronchitis, bronchiectosis and moderate diffuse pulmonary emphysema. Fibrinous pleuritis left upper lobe. Persistent thymus
(53) 44 A 143 D 45726	51 F. May	Carcinoma of gall bladder	Patient had a cholecystectomy 1 year previous. Given x-rays previously	Patient readmitted with epigastric pain vomiting. Developed painful area on calf of left leg. Treated with heat and elevation. While walking, patient suddenly cried out and fell to floor and died in 5 to 10 minutes. At autopsy left leg found to be larger than right.	Adenocarcinoma of gall bladder with metastases to colon, liver, subcutaneous fat and omentum. Multiple emboli right auricle, main pulmonary artery and lungs. Infarct of right lung. Adenoma of thyroid right and left lobes
(54) 44 A 190 D 49536	54 M. July	Tumor of right lung	Symptomatic	5 weeks prior to admission, patient developed slight cough accompanied by pain in right lower chest and relieved by adhesive plaster. Expectorated bloody sputum once. Had low grade fever and shortness of breath. Patient gradually went downhill and right arm became swollen. Suddenly while walking developed acute attack of dyspnea and cyanosis without pain and died in 10 minutes.	Massive pulmonary embolus (left main artery). Enlargement of right upper arm. Mesothelioma of right pleura with involvement of right lung. Compression of superior vena cava by surrounding tumor. Generalized arteriosclerosis.
(55) 45 A 56 D 59530	56 M. Feb.	Pains over left chest, anorexia, and moderate cough. Also had crampy feeling in calf of left leg. 3 days prior to admission, had severe pains in epigastrium	Symptomatic	Pains over precordium, worse on coughing and productive of blood-tinged sputum. Above symptoms and pain and tenderness of calves of legs persisted and left leg larger and warmer than right. Surgical consultant advised to defer ligation. Patient suddenly went into shock and died in 40 minutes	Phlebothrombosis of left posterior tibial vein. Massive pulmonary embolus. Small pulmonary emboli organizing. Old infarct of left lower lobe of lung. Recent infarcts with nemorrhages. Acute fibrinous pleuritis right. Early carcinoma of prostate.
(56) 46 A 22 75825	55 M. Feb.	Chronic congestive heart failure	Symptomatic	On 7th hosp. day complained of pains in left ankle. On 10th hosp. day patient had severe attack of dyspnea and died	Massive embolus of right main pulmonary artery and its branches Infarcts of lower lobe of lung. Generalized arteriosclerosis. Mural thrombi of auricles. Leg veins not examined. Multiple polyps of large intestine. Edema of lower extremities

Because we are concerned principally with the fatal forms of embolic disease, the cases in this group have been subjected to closer study. They are presented in tabular form in Table VI. In this group there were 26 males and 30 females, indicating no great preponderance in either sex. The age incidence was as follows: None in the age group of 0 to 20, 2 in the 20 to 30 group, 5 in the 30 to 40 group, 11 in the 40 to 50 group, 17 in the 50 to 60 group, 15 in the 60 to 70 group, 5 in the 70 to 80 group, none in the 80 to 90 group, one in the 90 to 100 group. Thus it would seem that the peak incidence occurred in the sixth decade of life, and that 43 of the 56 fatalities affected persons between the ages of 40 and 70 years.

As has been stated (Table II) fatal embolism occurred almost three times as frequently in surgical conditions as it did in medical. There were 43 fatalities in surgical cases as contrasted with 13 in medical. The operations which preceded the embolism covered a very wide range with no type of surgical procedure exhibiting a particular predisposition to embolus formation. The operations are listed in Table VII. It is of interest that no fatal emboli following childbirth were encountered among the cases that came to autopsy despite the not infrequent occurrence of puerperal thrombophlebitis. The one exception to this is a case following cesarean section, in which no thrombophlebitis occurred.

We were greatly concerned with the source of the embolism, the type of vein disease which produced the embolus and the clinical signs of danger from impending embolic accident. The source of the embolus was not found in 7 cases and there were 3 additional cases in which the source was not found, but the leg veins had not been examined. The deep veins of the lower extremities gave rise to the embolus in 43 of the remaining cases and the prostatic, pudendal, and left renal vein each contributed one fatal embolus. There were no fatal emboli from thrombi or phlebitides in the superficial veins of the lower extremities.

As already stated, 53 of the 56 fatal emboli arose from bland thrombi, and in only 3 cases in this series was the diagnosis of thrombophlebitis made. In these 3 cases, there was sufficient clinical evidence to support a diagnosis of deep vein thrombophlebitis of the lower extremities. In all of these, however, the embolus was apparently a portion of noninfected clot. It is entirely probable that in all 3 of these instances, a bland thrombus developed as a "tail-part" to a thrombophlebitic process, and that it was this noninflamed, nonadherent portion which broke loose to constitute the embolus. These 3 cases are abstracted below:

CASE 29. No. 39 A 258—C 66766. White male, aged 69 years, entered the hospital because of prostatic hypertrophy. A suprapubic cystotomy was done on October 9, 1939. On October 13, while sitting up in chair, patient had severe abdominal and back pain. On October 19, he complained of severe left chest pain, while lying in bed. Also, he had a rapid pulse at the same time. No swelling of legs was noted at this time. On November 5, 1939, the left leg became warm, painful, and edematous; the left thigh measured 2 centimeters greater in circumference than the right thigh. He was treated with rest, elevation, and heat. The electrocardiogram reading was compatible with that for pulmonary infarct. On November 10, he suddenly gasped for breath and died.

Pathological diagnosis: thrombophlebitis of left femoral vein, multiple large riding emboli of pulmonary arteries, old thrombi in smaller pulmonary arteries, myocardial fibrosis, benign prostatic hypertrophy, suprapubic cystotomy.

CASE 32. No. 41 M A 14—C 69428. White male, aged 41 years, entered the hospital for a bilateral herniorrhaphy. He developed a sore throat after operation. Twelve days postoperative the patient developed sharp pains, first in the right chest and later in the left chest, which were made worse by deep breathing or coughing. During the following weeks he had episodes of chest pain, fever, blood-tinged sputum, pleural friction rub, dyspnea, tachypnea, and cyanosis at times. On the 19th postoperative day swelling of the entire left leg was noted, the saphenous vein was palpable and tender and a red streak was present in the left thigh. About the 60th postoperative day the patient suddenly died with an attack of dyspnea, tachypnea, cyanosis, and shock.

Pathological diagnosis: Healed surgical incisions (2) for bilateral inguinal hernia; recent organizing and canalized thrombi in left common iliac, femoral, saphenous veins and deep vena comites of left leg with phlebosclerosis; multiple bilateral recent and organized pulmonary emboli; recent and organized pulmonary infarcts of lower lobes; organizing pleuritis left lower lobe; dilatation right ventricle; edema left lower leg.

CASE 38. No. 42 A 271—D 19413. White male, aged 58 years, entered the hospital for the surgical removal of a right adrenal cyst. Ten days after operation the patient developed pains in the right calf with an elevation of temperature. The right leg was found to be swollen and tender. Thrombophlebitis was diagnosed and x-ray treatments and immobilization were prescribed. Fever and swelling of the leg persisted and at times patient had chills. On the 20th postoperative day the patient had sudden, severe dyspnea with immediate pallor. He was given intravenous papavarine, atropine, intracardiac adrenalin, coramine, oxygen and artificial respiration, but the patient stopped breathing in 5 minutes and the heart stopped beating several minutes later.

Pathological diagnosis: absence of right suprarenal gland, thrombosis of right iliac and femoral veins, massive pulmonary embolus, acute and chronic passive hyperemia of lungs, myocardial fibrosis, uterolithiasis, multiple polyps of the rectum.

TABLE VII.—OPERATIONS IN WHICH DEATH WAS DUE TO PULMONARY EMBOLISM

Pelvic laparotomy		10
Cecostomy (peritonitis)		5
Prostatectomy		4
Cholecystectomy		3
Herniorrhaphy		3
Bowel resection		2
Thigh amputation		1
Gastroenterostomy		1
Adrenalectomy		1
Urethral transplantation		1
Thoracoplasty		1
Mastectomy		1
Cesarean section		1
Cystostomy		1
Colostomy		1
Cataract operation		1
Drainage of abscess		1
Biopsy of cervix		1
Radium insertion		
No operations		4
Immobilization of fractured femur	2	
Cellulitis of leg (diabetes)	1	
Bed rest for multiple contusion	1	

These 3 cases are the only ones in the entire series of fatal pulmonary emboli in which there was sufficient evidence of active thrombophlebitis of the deep veins of the lower extremities to warrant making that diagnosis. In all 3 cases the embolus apparently broke loose from a bland thrombus, which developed by extension from the thrombophlebitic segment of vein. These cases emphasize the extreme infrequency with which acute thrombophlebitis is associated with major pulmonary embolism. The very occasional embolic accident resulting from the propagation of a bland thrombus superimposed upon the inflamed thrombus, indicates the advisability of prophylactic anticoagulant therapy to prevent such secondary intravascular clotting.

The existence of vein disease, either phlebothrombotic or thrombophlebitic, was recognized clinically prior to the embolism in only 7 cases in this series. In the 49 remaining, vein disease was unsuspected. However, scrutiny of the charts reveals that edema was either noted clinically or was seen by the pathologist before the autopsy commenced in 21 cases. It is also noted that pain in the legs was mentioned either in the progress notes or the nurses' notes in the histories of 12 patients. Most of these occurred prior to the time when the significance of pain as an indication of thrombosis was appreciated. Premonitory, nonfatal pulmonary embolic attacks were recorded in 14 of the cases, whereas the 42 remaining had no warning infarcts prior to the fatal embolic accident. It must be recognized, as Aschoff showed many years ago, that occlusion of a pulmonary vessel will not result in infarction of the lung unless there is coexistent passive congestion. If the circulation is otherwise adequate the lung tissue will receive sufficient blood supply through the bronchial vessels to prevent infarct formation. The absence, therefore, of clinical signs of pulmonary infarction, does not mean that premonitory, nonfatal embolism has not occurred.

DISCUSSION

The results of this investigation lead to conclusions concerning the incidence and gravity of pulmonary embolism which differ considerably from many published reports. We believe the tendency to consider pulmonary embolism as an entity, without regard to the size of the embolus or the clinical conditions associated with its development, will lead to fallacious conclusions concerning the significance of this accident. When analyzed in terms of the role which the embolism plays in the causation of death, as has been done with the data here reported, the condition is placed in truer perspective. We have no wish to minimize the gravity of pulmonary embolism. However, the adoption of prophylactic or therapeutic measures must be weighed in terms of the actual hazard which this disease presents. As has been brought out in the figures cited, most of the pulmonary emboli encountered at autopsy are of but little or no clinical significance. The incidence of fatal embolism is much lower than many of the recent statistics imply. Here again it must be emphasized that the clinical diagnosis of pulmonary embolism carries a wide margin of error. In our own material many of the cases in which embolism was diagnosed were not confirmed at autopsy; conversely, a considerable number of the fatal emboli were not positively recognized before death occurred.

If our discussion is limited to the group of fatal emboli in which, presumably, the patient would have survived had not the embolus occurred, we find that this is a relatively infrequent accident. Our statistics indicate that over a 17 year period in a general hospital population of 800 beds, 56 fatal embolisms were found at autopsy. Since postmortem examinations were made in 56 per cent of the deaths, which have occurred in that period, it can be estimated that approximately 100 patients have died from pulmonary embolism alone during these 17 years, an average of about 6 per year, or 1 every 2 months. From the standpoint of the number of attending physicians on the staffs of the hospitals, the average number of embolic deaths over this 17 year period is a small fraction of 1 case per physician. This is quite different from some of the published individual series consisting of large numbers of cases. The statistics of Allen, from the Massachusetts General Hospital, are frequently quoted. Bilateral prophylactic femoral vein ligation was done in 458 patients.

In a comparable group of 458 patients undergoing the same types of operation, 55 cases of thromboembolic syndrome were noted, with 26 instances of fatal pulmonary embolism. There was one embolic death in the ligated series. Allen therefore estimates that 25 lives were saved by the ligations in this small series of patients. Admitting that Allen's series constitute a selected group of patients from the standpoint of age, it is nevertheless striking that in our surgical material 52,000 consecutive major operations would be required to furnish the number of embolic deaths which he encountered in 458 cases! Similarly, Thebaut and Ward recommend ligation of the inferior vena cava as the procedure of choice in thromboembolic disease. In their series of 36 cases there were 4 deaths, and 2 additional deaths followed bilateral femoral vein ligations. The mortality and morbidity under this regimen should be weighed against the dangers of the disease without operation, as revealed in our material.

The embolic cases in our series have been broken down according to whether the underlying illness was medical or surgical. It was found that in the less significant types of embolism, medical conditions outnumbered surgical almost two to one. In the fatal emboli, however, there were almost three times as many surgical cases as medical. It has been pointed out that the incidence of death from massive pulmonary embolism following operation is far lower than we have been led to believe. Of the 152,371 major surgical operations performed during the period of this study, there was an estimated total of 77 deaths from pulmonary embolism. This gives an incidence of 1 in 2,000 operations, and serves to indicate the actual postoperative risk from this complication. Whatever prophylactic and therapeutic measures are contemplated should be weighed in terms of the actual hazard which prevails. The relation of fatal embolus to antecedent vein disease aids in establishing the indications for the various therapeutic measures which have been advocated in thromboembolic disease.Inasmuch as almost all of the fatal emboli arose from bland thromboses, our data confirm the long held belief that thrombophlebitic vessels carry very little hazard of pulmonary embolism. On the other hand, the noninflamed, relatively asymptomatic bland thrombi constitute the source of real danger of embolic death.

The therapeutic implications from these facts seem clear. Phlebothrombosis is recognized as a serious threat of death from pulmonary embolism. Once formed, further propagation of the thrombus can be prevented by the use of anticoagulants. This does not, however, reduce the danger of embolism from the thrombus which is already present. The only safeguard against embolic death which we can offer in the presence of phlebothrombosis is the interruption of the venous trunk above the site of thrombosis.

Thrombophlebitis, on the other hand, carries with it very little risk of massive embolism other than that inherent in the possible bland thrombus which may extend by propagation from the phlebitic vein segment. Ligation, therefore, would not seem to be indicated. However, the use of anticoagulants to prevent the formation of a bland thrombus should serve to eliminate what little hazard exists in this condition. In view of the usual sudden onset of thrombophlebitis, its presence is announced by pain, fever, swelling, and tenderness in sufficient time to permit the administration of anticoagulants for the prevention of phlebothrombotic extension.

On the basis of these general rules we have adopted the following regimen in the management of these vein complications. If a diagnosis of phlebothrombosis is made on the presence of local findings in the lower extremities; namely, pain and soreness in the leg or foot, tenderness to pressure in the calf, pain on dorsiflexion of the foot (Homans' sign) or edema, ligation is done at the level of the superficial femoral vein on the side presenting the findings. If there are no evidences of phlebothrombosis on the opposite side, only a unilateral ligation is done. If present on both sides, bilateral ligation is obviously indicated. Should the indications for ligation be a premonitory pulmonary infarction, and should there be no local signs to indicate from which leg the embolus originated, one is compelled to do a bilateral ligation. As to the site for ligation, as stated, we consider the superficial

femoral vein just below its junction with the profunda femoris to be the preferred location from the standpoints of operative approach as well as of minimal subsequent circulatory impairment. If this portion of the femoral trunk is found to be thrombosed, one has the alternative of either attempting to remove the thrombus by suction or of making a higher incision and ligating at the iliac or even the vena cava level. To prevent thrombosis central to the ligature, anticoagulant therapy is indicated.

The management of thrombophlebitis presents entirely different indications. The risk of embolus, as has been said, from the thrombophlebitic vein segment is small and ligation, therefore, does not seem to be indicated. On the other hand, the occasional propagation of a nonadherent and noninflammatory thrombus with subsequent embolism does occasionally occur. To obviate such propagation, anticoagulant therapy is indicated. It is our plan to consider acute thrombophlebitis an infectious process and to treat it with chemotherapy and antibiotics as in any other acute infectious disease. In addition, anticoagulant therapy is instituted as soon as the thrombophlebitis develops. We give an initial injection of 50 milligrams of heparin intravenously every 4 hours for 48 hours. The oral administration of dicumarol is started simultaneously, and consists of a single dose of 300 milligrams the first day, 200 milligrams the second, and 100 milligrams the third day. From this time on the dosage is regulated by daily determinations of the prothrombin time. Further, to prevent thrombus formation, exercise and motion are encouraged, and the patient is allowed up with the support of an elastic bandage as soon as the temperature has become normal.

Perivertebral injection of the sympathetic ganglia has no direct application to the problem of embolism, and is therefore not discussed here. Its possible role in the alleviation of symptoms from thrombophlebitis is beyond the limits of this presentation.

SUMMARY AND CONCLUSIONS

An analysis has been made of all cases of pulmonary embolism found in consecutive postmortem examinations over a 17 year period. A total of 5,588 autopsies were performed in 9,980 deaths (56 per cent). The pulmonary emboli were divided according to their significance, as determined by the anatomical findings and a review of the clinical history, into three categories: those which were purely incidental findings, those which might have contributed toward the death of the patient, and those in which death was caused specifically by the embolus. These cases were further broken down with regard to the nature of the underlying illness, the source of the emboli, the character of the vein disease which preceded the embolus, and the variations according to sex, age, and season of the year. From these data the following conclusions are drawn:

1. Fatal embolism is less common than many recent studies would indicate. They were found in approximately 1 per cent of the autopsies. Although two-thirds of the embolic deaths occurred in surgical conditions, the mortality rate was 0.05 per cent, or 1 per 2,000 major operations.

2. Fatal emboli are almost always the result of a phlebothrombosis and almost invariably arise from the veins of the lower extremities. Thrombophlebitis rarely gives rise to embolism, and when it does, there is a bland thrombus superimposed upon the inflamed thrombus.

3. The hazard of pulmonary embolism in the presence of phlebothrombosis can be obviated only by interrupting the venous trunks above the level of the thrombus.

4. Thrombophlebitis does not require ligation but the use of the anticoagulants is indicated to prevent propagation of a bland thrombus with possible eventual embolism.

REFERENCES

1. Allen, A. W. Surg. Gyn. Obst., 1947, 84: 519–527.
2. Crutcher, R. R., and Daniel, R. A., Jr. Surgery, 1947, 23: 47–62.
3. De Takats, G., Beck, W. C., and Fenn, G. K. Surgery, 1939, 6: 339–367.
4. Ochsner, A., and De Bakey, M. South. Surgeon, 1939, 8: 269–290.
5. Thebaut, B. R., and Ward, C. S. Surg. Gyn. Obst., 1947, 84: 385–401.
6. Zimmerman, L. M. Surg. Gyn. Obst., 1935, 61: 443–457.

HEMOLYSIS DURING TRANSURETHRAL PROSTATIC RESECTION

CARL L. BIORN, M.D., and LAURENCE F. GREENE, M.D., Rochester, Minnesota

THE presence of excess amounts of free hemoglobin in the blood plasma of many patients immediately after transurethral prostatic resection has been recognized since Creevy and Webb reported its presence in a case in which oliguria and uremia developed after transurethral resection. They credited Emmett and McLaughlin with suggesting the possibility that sterile water used as an irrigating fluid during transurethral resection enters the circulation via prostatic veins and hemolyzes erythrocytes to an extent sufficient to damage the kidneys, exactly as does a transfusion with incompatible blood. Subsequently McLaughlin and his co-workers reported 3 cases in which oliguria developed after transurethral resection. They found that the pathologic lesion in the kidneys in 1 of these cases was similar to the lesions observed in cases in which hemoglobinemia developed after transfusion with incompatible blood. Later Landsteiner and Finch reported significant postoperative hemolysis in 10 of 15 patients who underwent transurethral resection.

The purpose of this paper is threefold. First, we intend to review the fundamental research and knowledge on which the present concept of hemoglobinemia and hemoglobinuria is based. Second, we wish to report the results obtained from our study of 100 patients on whom determinations of plasma hemoglobin were done immediately after transurethral resection. Last, we will interpret the results of our study on the basis of concepts of hemoglobinemia previously reviewed.

PATHOLOGIC PHYSIOLOGY OF HEMOGLOBINEMIA AND HEMOGLOBINURIA

Normal disposition of hemoglobin. Normally in the adult human being approximately 1.9 per cent of the circulating erythrocytes are destroyed each 24 hours; this destruction results in the liberation of between 7 and 8 grams of hemoglobin each day. Destruction of these erythrocytes with release of hemoglobin takes place within the cells of the reticulo-endothelial system. From this released hemoglobin the reticulo-endothelial cells metabolize bilirubin which is subsequently excreted by the liver. Theoretically, this process is an intracellular one and the hemoglobin does not escape into the circulating blood plasma. Actually, however, 100 cubic centimeters of normal human plasma contains 2 to 5 milligrams of free hemoglobin, that is, pigment derived perhaps from actual intravascular destruction of erythrocytes (44).

Disposition of free hemoglobin in the plasma. When an abnormal quantity of free hemoglobin is present in the plasma, the reticulo-endothelial cells continue to convert this pigment to bilirubin (44). However, if the hemoglobin is liberated faster than its conversion to bilirubin, then hemoglobinuria may occur. Similarly, if the amount of bile pigment formed is greater than can be excreted by the liver, retention of this product in the plasma results in hemolytic jaundice (5).

After intravenous injection of hemoglobin into dogs, Gilligan and associates found that less than 15 per cent of the total was excreted in the urine. Flink found when he injected larger quantities of hemoglobin intravenously that 25 to 40 per cent of the total hemoglobin in the plasma was so excreted. In one of their patients, O'Shaughnessy and his associates reported that 20 per cent of the total amount of circulating hemoglobin in the plasma was excreted in the urine. Supposedly the remaining 60 to 85 per cent of hemoglobin in the circulating plasma is metabolized by the reticulo-endothelial cells into bilirubin excreted later by the liver or retained in the plasma.

Hemoglobin is removed from blood plasma fairly rapidly. Gilligan and his co-workers injected hemoglobin into human beings and determined the length of time required to clear

From the Section on Urology, Mayo Foundation and Mayo Clinic.

the plasma of hemoglobin. They found that if the concentration of hemoglobin was 40 to 60 milligrams per 100 cubic centimeters of plasma, 5 hours were required for its value to return to normal; when the concentration was 130 to 225 milligrams per 100 cubic centimeters, 8 hours, and when it was 280 to 380 milligrams, 12 hours. In other words, the higher the concentration of hemoglobin in the plasma the longer the clearance time.

When hemolysis is extensive, the concentration of hemoglobin in the plasma rises until hemoglobin appears in the urine. A definite renal threshold for the excretion of hemoglobin has been determined for both man and dog. Monke and Yuile could not detect any hemoglobin in the urine of dogs as long as the level of plasma hemoglobin remained less than 80 to 100 milligrams per 100 cubic centimeters; when the concentration was higher, however, hemoglobin appeared in the urine. In man, Ottenberg and Fox found the renal threshold for the excretion of hemoglobin to be variable. In some persons hemoglobinuria developed when the level of hemoglobin was 110 milligrams per 100 cubic centimeters of plasma; in other persons even though the plasma hemoglobin attained levels of 200 to 288 milligrams per 100 cubic centimeters, no hemoglobin appeared in the urine. Similarly, Gilligan and his associates observed hemoglobin in the urine of those human beings who had concentrations of plasma hemoglobin of more than 135 milligrams per 100 cubic centimeters.

PATHOLOGIC RESULTS OF HEMOGLOBINEMIA AND HEMOGLOBINURIA

Our main interest in hemoglobinemia and hemoglobinuria is to determine whether the presence of free hemoglobin in plasma is harmful to patients undergoing transurethral resection. Some evidence concerning such a possibility may be gathered by reviewing the experiences of others who have injected hemoglobin into animals and man.

Results from injection of hemoglobin in man. Sellards and Minot and Ottenberg and Fox injected hemoglobin intravenously into human beings and noted either a mild reaction characterized by a chill with subsequent hot and cold flushes or no reaction at all.

O'Shaughnessy and associates, Fairley and Gilligan and co-workers observed untoward reactions characterized by chills, fever, nausea, abdominal cramps, pain in the back and loins and sensations of constriction in the chest following the intravenous injection of a solution containing hemoglobin. These symptoms parallel those noted in clinical hemolytic syndromes. However, no one has reported injecting sufficient hemoglobin into human beings to cause renal damage with oliguria similar to that in clinical hemolytic states. Amounts of hemoglobin sufficient to produce renal damage have been injected into animals.

Experimental production of renal damage by injection into animals of solutions containing hemoglobin. Ponfick produced hemoglobinuria by injecting heterologous blood into animals. He found pigmented casts deposited in the renal tubules of these animals.

Levy and Yorke and Nauss succeeded in reproducing renal damage similar to that observed in blackwater fever by injecting solutions of pure hemoglobin and homologous and heterologous laked blood into rabbits.

Baker and Dodds produced a marked rise in the values for nonprotein nitrogen in the blood of rabbits with acid urine by the intravenous injection of hemoglobin but noted no such phenomenon when the urine was alkaline. They concluded that precipitation of hemoglobin pigment in acid urine caused mechanical obstruction of renal tubules and resulted in suppression of urinary excretion.

DeGowin and co-workers (14, 15) showed that a high percentage of dogs with strongly acid urine succumbed to transfusions of large amounts of laked red blood cells while death did not follow similar injections if the urine of the animal was alkaline. The cause of death was uremia and pathologic examination of the kidneys disclosed changes similar to those found in other types of oliguria.

Most recently, Flink injected high dosages of hemoglobin intravenously into dogs that had either acid or alkaline urine and produced renal insufficiency in both. He found that the development of renal insufficiency in these dogs depended on the concentration of hemoglobin in the plasma immediately after the injection of the hemoglobin. An initial con-

centration of 3,700 milligrams of hemoglobin per 100 cubic centimeters of plasma or more was noted in all of the dogs in which renal insufficiency developed.

THE OLIGURIA SYNDROME

We will consider the oliguria syndrome, that is, primary oliguria and its associated symptoms in some detail because the coincidental occurrence of hemoglobinemia and oliguria in patients who have undergone transurethral resection has stimulated the belief that hemoglobinemia may be an important factor in causing the oliguria.

Oliguria following transurethral resection usually develops in cases in which the surgeon has encountered some difficulty such as rupture of the prostatic capsule, excessive hemorrhage or opening of periprostatic venous sinuses. In such cases, typical oliguria or anuria may develop. A progressive rise in the concentration of nitrogenous waste products in the blood occurs. Early the patient may suffer from anorexia, nausea and vomiting, but as the syndrome progresses these symptoms usually disappear and the patient feels relatively well. Many of these patients die of renal insufficiency, but some ultimately excrete urine and recover spontaneously.

The oliguria syndrome following transurethral resection is not different in any respect from the oliguria syndrome known to occur in a wide variety of acute illnesses. Oliguria is associated with pigment in the patients' blood and urine in blackwater fever (4, 24, 50), hemolytic transfusion reactions (2, 15, 16, 24), severe burns (46), obstetrical mishaps (39, 52), acute hemolytic anemia secondary to sulfonamide therapy (23) and the crush syndrome (8–10, 18). Maegraith, Havard and Parsons have examined the literature, however, and found that the syndrome develops in many conditions in which abnormal pigment may be absent from the urine. These may include the alkalosis of gastric tetany, septic abortion, cholera, yellow fever, diabetes, the hepatorenal syndrome, traumatic uremia, carbon monoxide poisoning, and pernicious anemia. Creevy also has pointed out that postoperative uremia may be due to acute pyelonephritis, prolonged severe hypotension, caused by hemorrhage, anesthesia or surgical shock, or to trauma to the ureteral orifices with resultant hydronephrosis.

Pathologic changes found in the kidney at necropsy in those cases in which patients died from this syndrome are strikingly similar no matter what the initial illness was (2, 7, 15, 26, 32). Characteristically, the glomeruli appear almost normal; some edema and cellular infiltration of the interstitial tissue may be present, but the outstanding changes are in the renal tubules. Degenerative changes occur especially in the loops of Henle and the distal convoluted tubules, and these may vary from mild vacuolization to necrosis and desquamation of cells. Granules of varying size may be noted in the epithelial cells of the convoluted tubules. Deposits of calcium in the degenerated tubules and signs of regeneration of epithelial cells have been found. At times a variable number of deeply pigmented casts appear in lumina of loops of Henle, distal convoluted tubules and the collecting tubules.

The mechanism of the development of this syndrome is not definitely known. The four main theories are (1) mechanical blockage of renal tubules, (2) a humoral nephrotoxic substance, (3) renal anoxia, and (4) renal arteriovenous shunts.

The concept of mechanical blockage by precipitation of hemoglobin pigment in the renal tubules is based on experimental work on the development of renal insufficiency after the injection of hemoglobin in animals with acid urine (3, 4). Theoretically, hemoglobin is thrown out of solution when the intratubular fluid becomes sufficiently acid and when simultaneously through absorption of water the concentration of sodium chloride is increased to about 1 per cent. These requirements are met in the lower nephron (that is, the distal loop of Henle and the distal convoluted tubules) and in the collecting tubules, the sites where cast formation is usually found (32).

Many investigators agree with the theory of mechanical obstruction but some believe that cast formation is secondary to the tubular epithelial degeneration and is not the cause of renal insufficiency per se (2, 16, 26). Experimentally, Yuile, Gold, and Hinds showed that hemic pigment is precipitated in tubules pre-

viously damaged by ischemia or by chemical poison. Their results indicate that precipitation of casts coincides with tubular damage. Bing has shown that renal insufficiency may develop without the precipitation of pigmented casts within the tubules. Flink produced renal insufficiency by injecting large doses of hemoglobin into dogs having either acid or alkaline urine. Clinically, fatal anuria following hemolytic transfusion reaction has occurred in the human being despite alkalinization of the urine and is no more common in blackwater fever in patients with acid than in those with alkaline urine (16, 24, 53),

The theory that some vasospastic or nephrotoxic substance, released into the circulation, induces renal damage and insufficiency is frequently mentioned but remains nebulous. DeGowin and co-workers (15) concluded that some factor other than tubular obstruction causes renal changes in this syndrome because in most of their 9 cases of "transfusion kidney" not enough tubules were obstructed to produce any important diminution in renal function. They postulated that a substance toxic to kidneys may be liberated by intravascular hemolysis.

According to the renal anoxia theory renal damage is caused by diminished supply of oxygen to the kidneys resulting from disturbance of renal blood flow which follows peripheral circulatory failure. The blood flow in the kidney can vary independently of the general circulation so that while the total volume of circulating blood may decrease in shock to approximately half of the normal value, the flow of blood through the kidney may decrease to one-tenth, one-twentieth, or even less of the normal flow (30, 43, 49). Various investigators including Phillips and associates and Corcoran and Page (11) have observed vasoconstriction of renal blood vessels during hemorrhagic shock to the point of almost complete absence of renal circulation. Such reduction of flow not only leads to diminished filtration force within the glomerular capillaries, but also to diminished peritubular circulation and reduction in essential oxygen supply with consequent tubular damage. The presence of an excess amount of hemoglobin in blood plasma also may contribute to this renal anoxia by producing vasoconstriction, since a definite shrinkage of the kidney has been detected immediately after the intravenous injection of laked red blood cells in the dog by Levy and of hemoglobin solution in the dog and frog by Mason and Mann and in the dog by Hesse and Filatov. Apparently the duration of ischemia is an important factor in determining the extent of renal injury. Van Slyke, for example, has shown that severe reduction of the renal blood flow during circulatory failure for a period of hours following hemorrhage is often followed by markedly impaired renal function and pathologic changes in the kidneys consisting chiefly of tubular necrosis and the presence of pigment casts in the tubules. These are changes not unlike those described in the oliguric syndrome of human beings. Supposedly, oliguria develops when tubular cells are damaged to such an extent that reabsorption of glomerular filtrate becomes unselective (17, 32, 42). In other words, the permeability of the necrotic cells is altered so that the osmotic pressure of the blood in the peritubular capillaries is able to draw back all, or practically all, of the normal glomerular filtrate and a scanty volume of urine is passed.

More recently Trueta has demonstrated that in certain oliguric states the blood passes from artery to vein through arteriovenous shunts in the kidney; in this manner the blood does not reach the renal cortex.

Thus, hemoglobinemia during transurethral resection, may be one of several factors inducing oliguria following resection by tubular obstruction, nephrotoxic effect or vasoconstriction.

HEMOLYSIS DURING TRANSURETHRAL PROSTATIC RESECTION IN 100 PATIENTS

Since hemoglobinemia in patients is known to follow transurethral resection we have been investigating the incidence of hemoglobinemia, the factors which may accompany or predispose to its development, and the possible postoperative ill effects in cases in which hemoglobinemia follows transurethral resection. This report is based on a study of 100 cases in which the concentration of plasma hemoglobin was determined after transurethral prostatic resection at the Mayo Clinic.

TABLE I.—VALUES OF PLASMA HEMOGLOBIN IN 100 CASES AFTER TRANSURETHRAL PROSTATIC RESECTIONS

Plasma hemoglobin, mgm. per 100 c.c.	Type of estimation		Total cases
	Quantitative	Qualitative	
501–1,000	6	0	6
301–400*	6	0	6
201–300	3	1	4
101–200	13	1	14
26–100	18	8	26
0–25	29	15	44

*No values from 401–500 mgm. in our series.

TABLE II.—POSTOPERATIVE VALUES OF PLASMA HEMOGLOBIN IN RELATION TO CONDITION FOR WHICH PROSTATIC RESECTION WAS PERFORMED

Condition	Plasma hemoglobin, mgm. per 100 c.c.	
	25 or less	More than 25
Benign prostatic hyperplasia	37	51
Carcinoma of prostate	5	4
Contracture of vesical neck	2	0
Vesical neoplasm with extension to prostate	0	1
Total cases	44	56

Method of study. The method of study has been as follows: The concentration of hemoglobin in the plasma was determined in 100 cases taken at random from those in which transurethral resections were performed at the clinic during the months of April to July, 1947. The incidence of hemoglobinemia in this series was calculated and any factors which may possibly accompany or predispose to hemoglobinemia were studied. These factors included the weight and nature of the tissue resected, the loss of blood and the difficulty of resection reported by the surgeon. Finally the series was analyzed for such possible postoperative ill effects secondary to hemoglobinemia as fever, chill, gastrointestinal symptoms and oliguria after resection.

The technique for determining the quantity of free hemoglobin pigment in the plasma was adapted from that of Flink and Watson. This method depends on conversion of derivatives of hemoglobin pigment to pyridine ferrohemochromagen whose absorption is measured with a photoelectric colorimeter which has been calibrated previously with known quantities of hemoglobin. In order to avoid artificially induced hemolysis, the blood must be collected carefully. We used a dry syringe with a close-fitting 19 gauge needle and took precautions to draw the blood slowly and carefully. Collapse of the vein wall on the needle, circulation of air bubbles in the blood, or too rapid withdrawal of the blood, all induce artificial hemolysis. The blood was then gently emptied into a graduated centrifuge tube which contained either 0.5 cubic centimeter of 3 per cent solution of sodium citrate or powdered heparin; the blood and anticoagulant were mixed by careful inversion and centrifuged. When heparin was used as an anticoagulant we obtained best results by dusting a small quantity on the portion of the syringe plunger which was in contact with the blood. We departed from Flink's technique in that we used a Kolmer colorimeter instead of an Evelyn and also used slightly different quantities of plasma and reagents. When larger amounts of plasma than 0.5 cubic centimeter were employed, we encountered difficulty with turbidity. Consequently, 0.1 to 0.5 cubic centimeter of plasma was placed in a colorimeter tube. To this was added sufficient amount of 1 per cent solution of ammonium hydroxide to bring the volume to 4.5 cubic centimeters. The volume was then increased to 6.0 cubic centimeters by the addition of 0.5 cubic centimeter of pyridine and 1.0 cubic centimeter of a 2 per cent solution of sodium hyposulfite ($Na_2S_2O_4$) freshly prepared in 1 per cent solution of ammonium hydroxide. A duplicate tube was set up in a similar manner with 0.5 cubic centimeter less of ammonium hydroxide to allow for the addition of 0.5 cubic centimeter of hydrogen peroxide and 5 minutes were allowed for decolorization. Then, after the center setting of the colorimeter was determined by use of the duplicate tube, the galvanometer reading of the unknown solution was determined. By applying this to the calibration curve, the hemoglobin content of the specimen was calculated.

Actually, hemolysis of any significant amount can be estimated by gross examina-

TABLE III.—POSTOPERATIVE VALUES OF PLASMA HEMOGLOBIN IN RELATION TO SURGICAL FACTORS

Plasma hemoglobin, mgm. per 100 c.c.	Cases	Average weight of tissue, gm.	Average blood lost, c.c.	Operative difficulties, per cent
501–1,000	6	36	365	100
301–400	6	30	165	67
201–300	4	41	497	75
101–200	14	41	298	50
26–100	26	25	242	19
0–25	44	20	153	20

tion of the patient's plasma after the blood has been centrifuged. The color of the plasma reflects the concentration of hemoglobin pigment. Thus, when expressed in approximate values, yellow plasma contains little or no hemoglobin, yellow with a slight pink tinge contains 25 to 30 milligrams; orange 30 to 65 milligrams, and pink 65 to 125 milligrams per 100 cubic centimeters. When more than 125 milligrams is present, the plasma is colored gradually deepening shades of red.

Results of investigation. Of the 100 patients in this series, 44 had 25 milligrams or less of hemoglobin per 100 cubic centimeters of plasma and 56 had levels above this figure (Table I). We used 25 milligrams per 100 cubic centimeters as a dividing point because gross hemolysis is first visible at this concentration and some of our determinations are based on gross observations only. (The actual upper limits of normal for plasma is 5 milligrams per 100 cubic centimeters.) The incidence of hemolysis in relation to the nature of the obstruction for which transurethral prostatic resection was performed is listed in Table II. The incidence of hemolysis was essentially the same for both benign and malignant lesions of the prostatic gland. Sterile water was used as the irrigating solution in all cases of this series. In a small group of patients not included in this study, however, both glycine and physiologic saline solution were used as irrigating solutions without appreciable postoperative hemolysis.

The operative factors which may accompany or predispose to hemoglobinemia are summarized in Table III. This table shows that the average weight of tissue removed in cases in which the level of plasma hemoglobin after operation was more than 25 milligrams per 100 cubic centimeters was greater than in cases in which it was 25 milligrams or less. However, the general rule that hemolysis occurs more commonly after removal of larger amounts of tissue is not invariable because in 2 cases of the series in which 9 and 7 grams of tissue were removed, the concentration of plasma hemoglobin after operation was 516 and 204 milligrams per 100 cubic centimeters, respectively. On the other hand, each of 4 patients in the group with little or no hemolysis had 50 grams or more of tissue removed.

In general, the average volume of blood lost at operation has been found to be higher in those cases in which the level of plasma hemoglobin was more than 25 milligrams per 100 cubic centimeters than in other cases. There were exceptions to this general rule also. Three patients who lost 45, 40, and 30 cubic centimeters of blood at operation had postoperative concentrations of hemoglobin of 384, 335, and 372 milligrams per 100 cubic centimeters of plasma, respectively. Conversely, 4 of those who did not have appreciable postoperative hemolysis lost more than 300 cubic centimeters of blood at operation.

The difficulty of resection and the level of postoperative hemoglobinemia appear to be definitely related. The surgeon encountered difficulty in 50 to 100 per cent of the cases in which the concentration of plasma hemoglobin after operation was more than 100 milligrams per 100 cubic centimeters. By contrast, the surgeon reported difficulty in only 20 per cent of all cases in which the postoperative level of plasma hemoglobin was less than 100 milligrams. The difficulties encountered by the surgeons in these cases are detailed in Table IV. This table shows that in all 6 cases in this series in which the postoperative concentration of plasma hemoglobin was more than 500 milligrams per 100 cubic centimeters, the operations were performed with difficulty. In 4 of the 6 cases operative bleeding was controlled with difficulty; in 1 case perforation of the urethra and in 1 opening of a definite venous sinus occurred. Similar difficulty was encountered during operation in 4 of the 6 cases in which the postoperative level

TABLE IV.—POSTOPERATIVE VALUES OF PLASMA HEMOGLOBIN IN RELATION TO SURGICAL DIFFICULTIES

	Plasma hemoglobin, mgm. per 100 c.c.					
	501–1,000	301–400	201–300	101–200	26–100	0–25
Total cases	6	6	4	14	26	44
Excessive bleeding	4			1	1	2
Perforation prostatic urethra or bladder	1*					1†
Opening of venous sinus	1	2	2	2	2	3
Pocketed gland		2	1		1	
Difficulty in cutting or engaging tissue				2		
Small vesical capacity				2		2
Continual vesical spasm					1	
Total cases with surgical difficulty	6	4	3	7	5	8

*Urethra †Bladder

of plasma hemoglobin was between 300 and 400 milligrams, in 3 of the 4 cases in which it was between 200 and 300 milligrams, and in 7 of the 14 in which it was between 100 and 200 milligrams. By contrast, the surgeon encountered difficulty during the operation in only 5 of the 26 cases in which the postoperative concentration of plasma hemoglobin was from 26 to 100 milligrams and in 8 of the 44 cases in which it was 25 milligrams or less. Excessive bleeding, opening of venous sinuses, and "pocketing" of the gland were the difficulties most frequently encountered.

Our investigation of possible postoperative reactions secondary to elevated concentrations of plasma hemoglobin in this series was confined to study of postoperative fever, chills, gastrointestinal complaints, and oliguria. A temperature of 101 degrees F. was chosen arbitrarily to represent a fever and only the fever and chill occurring on the first postoperative day were considered in this study because the febrile reaction caused by the accumulation of hemoglobin in plasma is known to appear within a short time after the development of hemoglobinemia. We considered the gastrointestinal symptoms including anorexia, nausea, and vomiting which occurred within the first few postoperative days; our estimation of oliguria was based on volume of urinary output during the first 4 days.

TABLE V.—POSTOPERATIVE VALUES OF PLASMA HEMOGLOBIN IN RELATION TO POSTOPERATIVE COMPLICATIONS

Plasma hemoglobin, mgm. per 100 c.c.	Cases	Chill	Fever	Gastrointestinal symptoms	Oliguria
501–1,000	6	0	0	6	0
301–400	6	0	1	5	0
201–300	4	0	1	3	0
101–200	14	0	2	8	0
26–100	26	0	2	15	0
0–25	44	0	11	16	1*

*Not true oliguria syndrome as described in text.

As shown in Table V, postoperative chill did not develop in any of the 100 cases. Eleven of the 44 patients who had 25 milligrams of hemoglobin or less had fever while only 6 of the 56 patients who had hemoglobinemia above this level had such fever. This comparison appears to show that concentrations of plasma hemoglobin found in this series do not cause postoperative fever and chill. On the other hand, the column of this table devoted to the incidence of gastrointestinal symptoms following transurethral resections shows that these symptoms occur more frequently in cases in which the postoperative level of plasma hemoglobin is high. For example, in more than 80 per cent of those cases in which the concentration of plasma hemoglobin was between 200 and 1,000 milligrams per 100 cubic centimeters postoperative anorexia, nausea, and vomiting occurred as compared with 37 per cent of those cases in which the level of plasma hemoglobin was 25 milligrams or less.

None of the patients in this series developed the oliguria syndrome regardless of the postoperative level of plasma hemoglobin. There was 1 death in this series and although the urinary output was low in this case, it obviously did not fall into the group of cases in which the oliguria syndrome as previously described occurred. This patient was a white man 77 years old who had arteriosclerotic heart disease, auricular fibrillation and rheumatoid polyarthritis, in addition to obstruction at the vesical neck. Risk of operation was considered great, but after 40 days of preparation, transurethral prostatic resection

TABLE VI.—URINARY OUTPUT OF 6 PATIENTS WHO HAD HIGH POSTOPERATIVE VALUES OF PLASMA HEMOGLOBIN

Patient	Plasma hemoglobin, mgm. per 100 c.c.	Daily urinary output on 3 postoperative days, c.c.			
		2nd	3rd	4th	Average
1	792	2,300	2,425	2,660	2,462
2	564	2,000	1,700	2,150	1,950
3	1,040	2,200	3,900	2,400	2,833
4	516	2,190	2,100	1,800	2,030
5	516	2,800	2,100	1,650	2,183
6	588	2,425	1,300	2,800	2,175

was performed. A diagnosis of contracture of the vesical neck, multiple prostatic calculi and chronic prostatic abscess was made at that time. During resection an old prostatic abscess was unroofed and a total of 2 grams of tissue was removed. The postoperative value of plasma hemoglobin was less than 25 milligrams per 100 cubic centimeters. The patient failed to respond well immediately after operation; cardiac decompensation and progressive renal insufficiency, manifested by oliguria and uremia, developed. The patient died from a high fever apparently caused by terminal bronchopneumonia 5 days after operation. Permission for necropsy was not granted. It was our impression that the oliguria was secondary to cardiovascular collapse.

The daily urinary output for the immediate postoperative days in those patients in whom the value of plasma hemoglobin was more than 500 milligrams is given in Table VI.

Studies of serum bilirubin were performed postoperatively in a small number of cases in which the higher levels of plasma hemoglobin were present. As expected, the van den Bergh reaction was indirect in each and the concentration of serum bilirubin was mildly elevated.

COMMENT

The incidence of hemolysis following transurethral resection in this series (56 per cent) compares favorably with that in similar series reported by others. Creevy found postoperative hemolysis in 19 of 27 cases (70 per cent) in which water was employed for irrigation at the time of resection. Landsteiner and Finch also reported hemolysis after 10 of 15 transurethral prostatic resections (66 per cent). Undoubtedly, if our criterion for hemolysis had been a concentration of hemoglobin of more than 5 milligrams per 100 cubic centimeters of plasma instead of 25 milligrams our results would approximate those of others even more closely.

We have shown that the operative loss of blood, the weight of tissue removed and the technical difficulty of resection, all tend to be greater in cases in which the postoperative concentration of plasma hemoglobin is increased. Creevy has shown that irrigating fluid composed of 4 per cent glucose may wash into the blood stream during resection to such an extent that the postoperative level of blood sugar may rise to more than 1,000 milligrams per 100 cubic centimeters. Similarly, Landsteiner and Finch labeled irrigating fluid used during transurethral resection with known quantities of sodium salicylate. They found a high concentration of sodium salicylate in the blood of a patient who also had a high concentration of plasma hemoglobin after resection and calculated that about 1,000 cubic centimeters of irrigating solution had washed into the blood stream during the procedure. That distilled water may cause hemolysis when injected intravenously has been shown by Krumbhaar on dogs and by Landsteiner and Finch on human beings. Therefore, it is reasonable to assume that when large amounts of tissue are resected, when excessive bleeding occurs, or when the resection is difficult, large amounts of irrigating fluid may wash into the circulation through venous sinuses in the prostatic bed and may induce hemolysis.

Our study of postoperative reactions secondary to accumulation of plasma hemoglobin following transurethral prostatic resection appears to show that gastrointestinal complaints are more frequent in patients with hemolysis. Of the patients with concentrations of hemoglobin of more than 200 milligrams per 100 cubic centimeters of plasma, approximately 85 per cent complained of postoperative nausea, vomiting or anorexia, whereas approximately 45 per cent of those with concentrations of less than 100 milligrams had such complaints. In other words, postoperative gastrointestinal symptoms occurred twice as

frequently in patients with high concentrations of plasma hemoglobin as in those with no significant hemolysis. Such a result coincides with observations made after the experimental injection of hemoglobin into human beings.

The results from our study of postoperative fever and chills are not consistent with past observations. The experimental injection of large doses of hemoglobin into human beings apparently causes fever and chill at times. Also, the febrile reaction accompanying such clinical syndromes as the hemolytic reaction following transfusion with incompatible blood is well known. Yet we found chills in neither the group of cases with hemolysis nor in the cases without hemolysis and fever occurred in a higher percentage of cases without hemolysis than in those with significant hemolysis. The many factors causing febrile reactions following transurethral prostatic resection undoubtedly account for this discrepancy.

The patient in this series who had postoperative oliguria did not have significant hemoglobinemia following resection. This does not prove that hemoglobinemia does not induce oliguria. It has been stated previously that postoperative oliguria is based on many factors of which hemoglobinemia may be only one. Actually, the levels of plasma hemoglobin reported in the literature to induce renal insufficiency are higher than the concentrations in the cases in our series. In dogs, Flink injected sufficient hemoglobin to produce concentrations of at least 3,700 milligrams of hemoglobin per 100 cubic centimeters of plasma before renal insufficiency developed. In human beings, there is evidence to indicate that the same high levels of plasma hemoglobin are necessary before renal insufficiency develops. Comparison is difficult, however, because many of the published reports concerning the development of renal insufficiency following hemoglobinuria either fail to give the level of plasma hemoglobin at its height, prior to the onset of oliguria, or do not mention the time interval between the onset of hemoglobinuria and the determination of plasma hemoglobin. We have previously stated that hemoglobin is rapidly removed from the blood stream; yet Altschule and Gilligan found the plasma hemoglobin to be 500 milligrams per 100 cubic centimeters 24 hours after the onset of hemoglobinuria in a patient in whom the concentration of nonprotein nitrogen rose to 90 milligrams per 100 cubic centimeters of blood but who recovered. Fox and Ottenberg described 4 cases of hemolytic anemia and hemoglobinuria due to sulfonamides in which the hemoglobin content of the plasma ranged from 400 to 1,700 milligrams per 100 cubic centimeters. Two patients died from renal insufficiency but the time interval between onset of hemolysis and determination of the level of plasma hemoglobin varied between 12 and 48 hours. Fairley and Bromfield observed 3 patients who died of anuria from blackwater fever; the concentrations of plasma hemoglobin were 3,600, 4,610, and 5,140 milligrams per 100 cubic centimeters. By way of contrast with these figures, only 6 of the 100 patients in our series had more than 500 milligrams of hemoglobin per 100 cubic centimeters of plasma immediately after resection; of these, 1 had a level of approximately 1,000 milligrams. This could indicate that concentrations of plasma hemoglobin commonly attained during transurethral prostatic resection are not sufficiently high to cause renal insufficiency. However, Creevy has advanced the opinion that in order to produce renal insufficiency in elderly men who have lost blood while under anesthesia, high values of plasma hemoglobin may not be necessary.

SUMMARY AND CONCLUSIONS

Some fundamental concepts of hemoglobinemia and hemoglobinuria were reviewed to interpret the results of a study of plasma hemoglobin in 100 cases of transurethral prostatic resection performed at the Mayo Clinic.

The incidence of hemoglobinemia following transurethral resection in this series was 56 per cent. This incidence is somewhat lower than that previously reported, perhaps because our criterion for hemoglobinemia was based on a higher concentration of plasma hemoglobin than others have employed. Factors during resection which accompanied or may have predisposed to postresection hemoglobinemia in this series were the weight of tissue resected, volume of operative blood lost and the difficulty of resection.

Postoperative gastrointestinal symptoms were more common among those patients of this series who had high concentrations of plasma hemoglobin than among those who did not have any hemolysis. Hemolysis did not appear to increase the incidence of postoperative fever and chills in this series.

Concentrations of plasma hemoglobin per se commonly attained during transurethral prostatic resection usually are not sufficiently high to produce anuria.

REFERENCES

1. ALTSCHULE, M. D., and GILLIGAN, D. R. Arch. Int. M., 1941, 68: 957–978.
2. AYER, G. D., and GAULD, A. G. Arch. Path., 1942, 33: 513–532.
3. BAKER, S. L., and DODDS, E. C. Brit. J. Exp. Path., 1925, 6: 247–260.
4. BARRATT, J. O. W., and YORKE, WARRINGTON. Ann. Trop. M. Parasit., Liverp., 1909, 3: 1–256.
5. BEST, C. H., and TAYLOR, N. B. The Physiological Basis of Medical Practice. 4th ed., p. 50. Baltimore: Williams & Wilkins Co., 1945.
6. BING, R. J Bull. Johns Hopkins Hosp., 1944, 74: 161–176.
7. BORDLEY, JAMES, III. Arch. Int. M., 1931, 47: 288–315.
8. BYWATERS, E. G. L., and BEALL, D. Brit. M. J., 1941, 1: 427–432.
9. BYWATERS, E. G. L., and STEAD, J. K. Q. J. Exp. Physiol., 1944, 33: 53–70.
10. CORCORAN, A. C., and PAGE, I. H. J. Lab. Clin. M., 1945, 30: 351–352.
11. Idem. Arch. Surg., 1945, 51: 93–101.
12. CREEVY, C. D. J. Urol., Balt., 1947, 58: 125–131.
13. CREEVY, C. D., and WEBB, E. A. Surgery, 1947, 21: 56–66.
14. DEGOWIN, E. L., OSTERHAGEN, H. F., and ANDERSCH, MARIE. Arch. Int. M., 1937, 59: 432–444.
15. DEGOWIN, E. L., WARNER, E. D., and RANDALL, W. L. Arch. Int. M., 1938, 61: 609–630.
16. DE NAVASQUERZ, S. J. Path. Bact., 1940, 51: 413–425.
17. DUNN, J. S., and POLSON, C. J. J. Path. Bact., 1926, 29: 337–352.
18. DUNN, J. S., GILLESPIE, MARJORIE, and NIVEN, J. S. F. Lancet, Lond., 1941, 2: 549–552.
19. FAIRLEY, N. H. Brit. M. J., 1940, 2: 213–217.
20. FAIRLEY, N. H., and BROMFIELD, R. J. Tr. R. Soc. Trop. M. Hyg., 1934, 28: 141–156.
21. FLINK, E. B. J. Lab. Clin. M., 1947, 32: 223–261.
22. FLINK, E. B., and WATSON, C. J. J. Biol. Chem., 1942, 146: 171–178.
23. FOX, C. L., JR., and OTTENBERG, REUBEN. J. Clin. Invest., 1941, 20: 593–602.
24. FOY, HENRY, ALTMANN, ALFRED, BARNES, H. D., and KONDI, ATHENA. Tr. R. Soc. Trop. M. Hyg., 1943, 36: 197–238.
25. GILLIGAN, D. R., ALTSCHULE, M. D., and KATERSKY, EVELYN M. J. Clin. Invest., 1941, 20: 177–187.
26. GOLDRING, WILLIAM, and GRAEF, IRVING. Arch. Int. M., 1936, 58: 825–845.
27. HESSE, E., and FILATOV, A. Zschr. ges. exp. Med., 1933, 86: 211–230.
28. KRUMBHAAR, E. B. J. Am. M. Ass., 1914, 62: 992–993.
29. LANDSTEINER, E. K., and FINCH, C. A. N. England J., M., 1947, 237: 310–312.
30. LAUSON, H. D., BRADLEY, S. E., and COURNAND, ANDRE. J. Clin. Invest., 1944, 23: 381–402.
31. LEVY, L. Deut. Arch. klin. M., 1904, 81: 359–382.
32. LUCKE, B. Mil. Surgeon, 1946, 99: 371–396.
33. MCLAUGHLIN, W. L., HOLYOKE, J. B., and BOWLER, J. P. J. Urol., Balt., 1947, 58: 47–60.
34. MAEGRAITH, B. G., HAVARD, R. E., and PARSONS, D. S. Lancet, Lond., 1945, 2: 293–296.
35. MASON, J. B., and MANN, F. C. Am. J. Physiol., 1931, 98: 181–185.
36. MONKE, J. V., and YUILE, C. L. J. Exp. M., 1940, 72: 149–165.
37. O'SHAUGHNESSY, L., MANSELL, H. E., and SLOME, D. Lancet, Lond., 1939, 2: 1068–1069.
38. OTTENBERG, REUBEN, and FOX, C. L., JR. Am. J. Physiol., 1938, 123: 516–525.
39. PAXSON, N. F., GOLUB, L. J., and HUNTER, R. M. J. Am. M. Ass., 1946, 131: 500–504.
40. PHILLIPS, R. A., DOLE, V. P., HAMILTON, P. B., EMERSON, KENDALL, JR., ARCHIBALD, R. M., and VAN SLYKE, D. D. Am. J. Physiol., 1946, 145: 314–336.
41. PONFICK. Virchows Arch., 1875, 62: 273–335.
42. RICHARDS, A. N. Tr. Ass. Am. Physicians, 1929, 44: 64–67.
43. RICHARDS, D. W., JR. Bull. N. York Acad. M., 1944, s. 2, 20: 363–393.
44. ROSS, J. F. N. England J. M., 1945, 233: 691–766.
45. SELLARDS, A. W., and MINOT, G. R. J. Med. Res., 1916, 34: 469–494.
46. SHEN, S. C., and HAM, T. H. N. England J. M., 1943, 229: 701–713.
47. TRUETA, JOSEP, BARCLAY, A. E., DANIEL, P. M., FRANKLIN, K. J., and PRICHARD, MARJORIE M. L. Studies of the Renal Circulation. P. 126. Springfield: Charles C Thomas, 1947.
48. VAN SLYKE, D. D. Quoted by Goodpastor, W. E., Levenson, S. M., Tagnon, H. J., Lund, C. C., and Taylor, F. H. L. Surg. Gyn. Obst., 1946, 82: 652–670.
49. VAN SLYKE, D. D., PHILLIPS, R. A., HAMILTON, P. B., ARCHIBALD, R. M., DOLE, V. P., and EMERSON, K., JR. Tr. Ass. Am. Physicians, 1944, 58: 119–127.
50. WAKEMAN, A. M., MORRELL, C. A., EISENMAN, ANNA J., SPRUNT, D. L., and PETERS, J. P. Am. J. Trop. M., 1932, 12: 407–439.
51. YORKE, WARRINGTON, and NAUSS, R. W. Ann. Trop. M., Parasit., Liverp., 1911, 5: 287–312.
52. YOUNG, JAMES. Brit. M. J., 1942, 2: 715–718.
53. YUILE, C. L. Physiol. Rev., 1942, 22: 19–31.
54. YUILE, C. L., GOLD, M. A., and HINDS, E. G. J. Exp. M., 1945, 82: 361–374.

EDITORIALS

SURGERY
Gynecology and Obstetrics

FRANKLIN H. MARTIN
Founder and Managing Editor
1905–1935

LOYAL DAVIS, Editor

Associate Editors
SUMNER L. KOCH MICHAEL L. MASON
M. E. SPENCER, Assistant Editor
JAMES T. PRIESTLEY, Associate, Editorial Staff

MARCH, 1949

PHYSIOLOGIC METHODS IN THE DIAGNOSIS OF CONGENITAL HEART DISEASE

THE introduction of surgical procedures for the correction of congenital malformations of the heart and great vessels by Blalock, Craaford, and Gross and their associates has placed emphasis on the correct preoperative diagnosis of these lesions. A great many of these malformations can be correctly diagnosed by fluoroscopic and physical examination. In borderline cases, however, more elaborate procedures are necessary. These include visualization of the heart and great vessels with radio-opaque material (angiocardiography) and physiological procedures.

The most useful physiological studies are catheterization of the heart, measurement of pulmonary capillary flow, a standard exercise test, and oximetry.

Venous catheterization of the heart is of particular value. The fullest amount of information is obtained if three criteria are followed: (1) The position of the catheter should be closely followed under the fluoroscope. (2) Blood samples and pressures should be obtained by means of the catheter from the cardiac cavities, from blood vessels coursing to and from the heart, and from a peripheral artery. The oxygen content of these samples should be determined. Pressures should be recorded with differential manometers. The measurement of mean pressures with saline or mercury manometers does not give sufficient information, since the height of the diastolic pressure is frequently of particular diagnostic importance. (3) The volume of blood flowing through the pulmonary artery (pulmonary artery flow), the intracardiac shunt, and the systemic vessels (systemic blood flow) should be calculated by the Fick principle from the oxygen content of the blood samples. The main diagnostic value of these calculations lies in the recognition of reduced pulmonary artery flow and in the estimation of the volume and the direction of the intracardiac shunt. Of particular importance is the calculation of the effective pulmonary blood flow. This represents the amount of mixed venous blood which reaches the pulmonary alveoli. The ratio of the effective pulmonary blood flow to the total systemic flow determines the degree of oxygen saturation in arterial blood. The Blalock-Taussig operation is beneficial because this ratio is increased through the construction of an artificial ductus.

In the surgical laboratory of the Johns Hopkins Hospital catheterization of the heart has now been performed on approximately eight hundred individuals with congenital heart disease. In five of these, air emboli to the brain occurred during the catheterization.

However, all symptoms disappeared within 24 hours and there was no residual damage.

The pulmonary capillary flow is determined by a method involving the equilibration of carbon dioxide with pulmonary capillary blood, the sampling of carbon dioxide content in alveolar air, and the determination of carbon dioxide production. While sampling of pulmonary artery blood permits the calculation of the pulmonary artery flow only, the carbon dioxide equilibration method measures the total amount of blood perfusing the lungs (pulmonary capillary flow). By comparing pulmonary artery with pulmonary capillary flow the flow through the collateral vessels or through an artificial or congenital ductus arteriosus may be estimated.

The standard exercise test compares the ratios of the oxygen consumption to respiratory minute volume during a standard exercise test and at rest. Normally the oxygen consumed per liters of ventilation increases from rest to exercise. In conditions in which pulmonary flow is fixed (e.g., pulmonary stenosis) this ratio usually declines. The test is easily performed and requires no special preparation.

The oximeter is an instrument which measures the oxygen saturation in peripheral arterial blood by means of a photoelectric cell attached to the pinna of the ear. The original Millikan instrument has been greatly improved by the more accurate models designed by Woods and Geraci and by R. T. Cox. The newer models permit the measurement of the arterial oxygen saturation within 5 per cent accuracy. The fact that the peripheral oxygen saturation falls during exercise in the presence of a venous arterial shunt can be demonstrated with great ease by oximetry. This is usually carried out simultaneously with the standard exercise test. Furthermore, the oximeter is useful in differentiating anoxemia due to venous-arterial shunts from arterial unsaturation due to oxygen transfer difficulties resulting from pulmonary disease. In the latter case the oxygen saturation rises within one minute to full saturation when 100 per cent oxygen is inhaled. In the presence of a venous-arterial shunt, on the other hand, the rise in oxygen saturation will extend over several minutes and full arterial oxygen saturation is rarely obtained.

The results of these tests in tetralogy of Fallot show a decrease in pulmonary artery flow, an intracardiac shunt predominantly directed from right to left, and usually evidence of marked collateral circulation to the lung. The systolic pressure in the right ventricle is significantly elevated above that in the pulmonary artery. The exercise test shows a fall in the oxygen consumed per liters of ventilation and a decline in the peripheral arterial oxygen saturation. On the breathing of pure oxygen the peripheral arterial oxygen saturation rises over a period of several minutes and full saturation is not reached.

In Eisenmenger's complex and in a great majority of auricular or ventricular septal defects the pulmonary artery pressure is elevated. This is probably the result of arteriolar changes in the pulmonary vessels. As a result of the increased resistance in the pulmonary vascular bed, the overall direction of the intracardiac shunt may be from right to left.

Elevation of the pulmonary artery pressure due to increased resistance in the pulmonary bed is also frequently encountered in auricular or ventricular septal defects. In the presence of an auricular septal defect the oxygen content of right auricular blood exceeds that of vena caval blood. With a ventricular septal defect the oxygen content of right ventricular blood exceeds that of right auricular blood. During the standard exercise test the oxygen consumed per liters of ventilation usually in-

creases and the oxygen saturation of peripheral arterial blood falls.

Recent advances in the surgical treatment of transposition of the great vessels by Blalock and his associates have focused the interest of pediatricians and surgeons on this malformation. The intracardiac hemodynamics in transposition of the great vessels differ from those described for the tetralogy of Fallot and related conditions. In transposition the pulmonary arterial blood flows from the left ventricle through the lungs into the left auricle, while the systemic blood courses from the right ventricle into the aorta through the systemic circulation and back into the right auricle. If this malformation is to be compatible with life, oxygenated blood must reach the aorta either through a septal defect or a patent ductus arteriosus. However, the volume of oxygenated blood shunted into the systemic circulation must be balanced by an equal volume of unsaturated blood entering the pulmonary circulation, since a unilateral shunt would lead rapidly to a diminishing blood volume in either the pulmonary or the systemic circulation. The volume of the shunted blood in either direction equals the effective pulmonary blood flow. The practical importance of these considerations lies in the fact that any surgical correction of transposition which involves the creation of a unilateral shunt must be balanced by an equal and opposite shunt.

In patent ductus arteriosus, the blood oxygen content in the pulmonary artery exceeds that in the right ventricle. The blood pressure in the pulmonary artery may be normal or slightly elevated. The oxygen consumed per liters of ventilation and the oxygen saturation in peripheral arterial blood remain constant during the standard exercise test.

The physiological procedures described are of particular value in the recognition of diminished pulmonary artery flow and of decreased or increased pulmonary arterial pressures. In most instances they are helpful in identifying and locating intracardiac or extracardiac shunts. Furthermore, changes in hemodynamics produced by operative procedures can be quantitatively evaluated. As the field of cardiac surgery expands into the realm of acquired heart disease, physiological studies will be of increasing importance in supplying the surgeon with essential criteria for operative intervention. RICHARD J. BING.

EXSTROPHY OF THE BLADDER

EXSTROPHY of the bladder is one of the rare congenital anomalies, occurring once in 40,000 births, which is amenable to surgical treatment, but the fact that there have been about seventy different surgical procedures described for its correction indicates that there must be many points of interest about the technique and results of the surgical methods which remain unsatisfactory.

The optimal time for operation is one of the points for discussion. When one considers that from a statistical point of view half of these patients are dead by their tenth year and two-thirds are dead by their twentieth year, it simply indicates that whatever is done for them must be carried out before adolescence, and more particularly before the tenth year. In recent years it has been recommended that these operations be done during the first twelve months of the patient's life, under the supposition that an infant tolerates trauma unusually well and that the anomaly should be corrected before any recurrent renal infection develops. In evaluating this point one should remember that perhaps it is better to delay until the patient has learned bowel control. Also, this condition is not considered a surgical emergency as is pyloric stenosis, tracheobronchial fistula, strangulated umbili-

cal hernias, and so forth, so that one can conceivably wait until the fourth or fifth year when the anatomic structures are larger and anastomosis can be more satisfactorily and accurately done. The preparation of the bowel for ureterosigmoidal anastomosis can also be done more easily and completely. Since the results depend almost entirely on the character of the anastomosis, these structures should be of such size as will enable one to approximate them accurately without tension. I doubt if these conditions, which are so vital to the conduct of the operation and to the future health of the patient, are present before the patient is five years of age.

Bilateral ureterosigmoidal anastomosis and cystectomy are regarded as the proper procedures for surgical correction of exstrophy of the bladder, to be followed by any plastic procedures which may be required on the external genitalia of either sex. Whether this ureteral transplantation should be done in one stage or two stages has been a matter of considerable debate. The decision depends, it would seem, on the type of anastomosis which is used and on the fact that antibiotics and penicillin are available in the preparation of the sigmoid and for the prevention of postoperative infection of the urinary tract. In earlier years a two stage operation, either extraperitoneal or intraperitoneal, was generally regarded as the proper procedure. More recently with improvement in the technical procedures of the anastomosis and in preparation of the bowel the one stage operation is favored.

The object of the operation is to secure an adequate urinary sinus between each ureter and the sigmoid without subsequent ureteral obstruction or retrograde contamination of the upper part of the urinary tract. It is on account of these two factors particularly that so many operations have been devised, directed at the improvement of the ureterosigmoidal anastomosis. Obviously the anastomosis can be more perfectly and accurately accomplished by the transperitoneal approach because to carry out this procedure, it is vital that the sigmoid be accurately placed adjacent to the ureter on each side and that the ureter be placed in the bowel without tension and without fixation. When tension and fixation of the ureter occur at the point of union to the bowel there will be interference with its delicate blood supply and the incidence of ureteral fistula increases. Also the rhythmic contraction of the ureter for the proper expulsion of the urine into the bowel will not be normal, and there will be subsequent obstruction and ureteral dilatation with infection of the urinary tract. Under these circumstances then the most favorable situation is where the ureter is placed within the bowel devoid of any sutures, catheters, or guides. This can be accomplished by the standard Coffey-Mayo technique with these exceptions; the ureter is gently pulled into the bowel for a distance of 3 to 4 centimeters and is held firmly until the bowel can be fixed to the parietal peritoneum for a distance of at least 4 centimeters above and below the point where the ureter enters the wall of the sigmoid. The bowel is fixed firmly to the peritoneum so that the ureter goes directly into the bowel without tension or any fixation. The peritoneum, if properly placed with relation to the bowel, will close any defect in the bowel within a few hours and will prevent any leakage of urine or intestinal contents.

When one reviews the deaths after ureterosigmoidostomy for exstrophy, it is noted that 50 per cent of the deaths in the hospital are due to pyelonephritis, ureteritis with or without gangrene, and peritonitis; and that uremia and pyelonephritis with stones or hydronephrosis or both account for 65 per cent of the deaths after the patients leave the hospital.

Patients who have practically normal pyelograms and ureterograms within a few months subsequent to transplantation rarely have any attacks of infection of the upper part of the urinary tract, a fact which must indicate that the surgical procedure which was utilized approached at least the desired requirements. Further evidence that delayed urinary complications are directly attributable to the character of the anastomosis is shown by the fact that if a kidney becomes functionless the left one is involved three times more commonly than the right kidney and the correct application of the sigmoid to the peritoneum on the left side without tension on the ureter is three times more difficult to accomplish than on the right side.

Obviously, then, the surgical problem in managing exstrophy of the bladder is to select the favorable time for surgical intervention, to give strict attention to securing a ureterosigmoidal anastomosis without tension or fixation of the ureter and to require periodic studies of the upper part of the urinary tract of the postoperative patients for from three to five years.

If in a few months or years ureteral obstruction appears and becomes progressive with a gradual loss of renal function, permanent nephrostomy or ureterostomy is the operation of choice and will add a number of years to the patient's life expectancy.

A good functioning skin ureterostomy is more serviceable to the patient than a nephrostomy because the patient can change the catheters himself when necessary and can adjust them to the proper level within the renal pelvis to obtain efficient drainage. A catheter which does not extend to the renal pelvis will have urine leaking around it.

Good skin ureterostomies are difficult to produce and this procedure should not be undertaken by anyone who is not familiar with the conditions which may arise that will cause complete failure of the operation, such as sloughing and retraction of the end of the ureter below the abdominal wall; pressure from the catheter or an abscess in the wall of the ureter may produce a ureteral fistula, thereby ruining the operation.

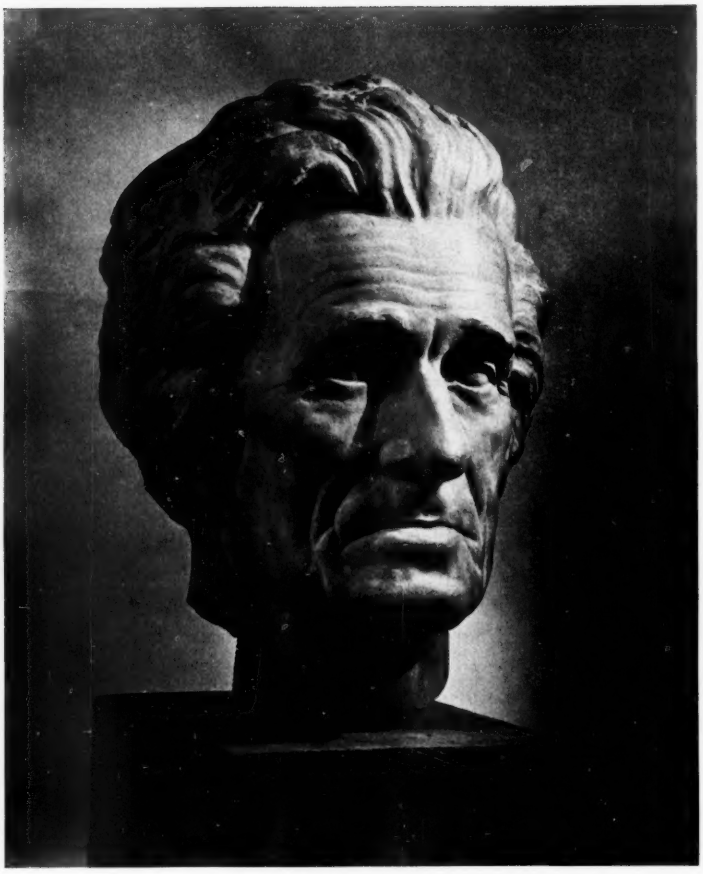
A nephrostomy is a less complicated procedure and can be done subsequently if a skin ureterostomy has for any reason been a failure. It is more troublesome to the patient because some one must change the nephrostomy tubes and dress the area for him. A nephrostomy is practically a defect-proof operation and can be performed by most surgeons interested in this field of surgery. Even so, I feel it should be emphasized that to secure a good functioning nephrostomy it should be so placed that it goes directly down from the skin surface through the kidney and into its pelvis. Should the pelvis be a bifid one or should there be a complete duplication then double nephrostomies may be necessary, but such information must be available before the operation is begun.

These two surgical procedures should be considered as a reserve which may be utilized subsequently to prolong the life and comfort of patients if for any reason the ureterosigmoidostomy has become defective with consequent destruction of renal tissue and function.

The use of antibiotics and penicillin during preparation for, and subsequently to, surgical treatment will increase life expectancy to a considerable degree. Certainly the future for these patients is promising, especially when one considers that without these drugs 50 per cent of patients were alive twenty-five to thirty years after operation.

VIRGIL S. COUNSELLER.

UNIVERSITY OF MICHIGAN LIBRARIES



Andrew Jackson, 1767-1845

The Gentleman from Tennessee.—Frances Tomlinson Gardner.

Photograph of head of Andrew Jackson modelled from life by John Frazee. Courtesy Art Museum, Princeton University.

THE SURGEON'S LIBRARY

THE BOOK SHELF

THE GENTLEMAN FROM TENNESSEE

FRANCES TOMLINSON GARDNER, San Francisco, California

ANDREW JACKSON is a legend. His political career, his army life, and his domestic career have been explored as thoroughly as the personal affairs of Hamlet's father. His biographers, although they have meticulously recorded all these things, have touched on the subject of his health and physique with the small interest of casual reporters. Andrew Jackson was made of the usual blood and bone but the one was thin and the other fragile. No structure ever endured under greater handicaps than the frame that supported the brain of the astonishing, the determined, the invincible gentleman from Tennessee.

He was normally born to sturdy pioneer parents in the Waxhaws Settlement of North Carolina in March, 1767. His father was recently dead of an injury resulting from trying to lift a fallen tree single handed. His energetic mother died of typhus when Andrew was fifteen. His two brothers were robust and died of causes unrelated to heredity. In Andy's early youth his only recorded skirmish with disease was an attack of something called "The Big Itch," of which it was said that it itched one very much all over.

His small taste of the Revolutionary War ended in his capture by the British who imprisoned the boy and his brother, Robert, in a blockhouse, near Camden. Due to a refusal to black the boots of a demanding British officer Andrew received the saber cuts on wrist and temple which were still prominent when the old man died sixty-four years later. Hidden, but of far deeper significance, was the rancor which settled in the inner Jackson and which colored every thought and action toward the British most of the days of his life.

Still in bandages from the assault, he, as well as his brother, caught the smallpox which swept the unhygienic quarters in which they were housed. News of the epidemic reached Mrs. Jackson and she came to prevail upon the British to release the presumably dying children to her custody so that she could take them home to nurse them. The British gladly consented since, for them, it meant two invalids less, and Mrs. Jackson loaded Robert, the sicker of the two, on her only available horse. Andrew, horseless, and hardly less ill, walked the entire forty miles back to the cabin in the Waxhaws. Robert did not live to get home and Andrew, soaked by a pouring rain and with his smallpox "driven in" arrived in a raging fever and delirium. To everyone's surprise he eventually recovered and no one paid much attention to the long siege of "fever n'ague" which he endured after the disease had subsided. From this time began the underscoring of "low fever," "intermittent fever" or, "fever" which was seldom absent from Jackson's own mention of his health. In the fastnesses of North Carolina malaria was endemic. Who was he to escape?

At fifteen he was long, skinny, and sallow. His manners were bad and his language deplorable. While he was at school, though he was as thin as a pencil and as fragile as a pipestem, he would fight, at the drop of an epithet, anyone who had the misfortune to annoy him. He seldom won since everybody else was stronger and heavier, but it was not important to him. Nor was it important that the same boy might have beaten him unmercifully the day before. He learned very young that offense was his best defense and, through it he did manage, at considerable physical expense, to keep at a minimum, unkind comment about his embarrassing physical defect. It must be admitted that, from infancy to manhood, poor Andrew was a drooler. The condition was bad enough when he was calm but when he became excited it was gushingly profuse. Since he could not swallow fast enough to dispose of the quantities of saliva with which his overactive parasympathetic nervous system afflicted him, he could only defend his right to it. Since it was a vicious circle, he spent much of his time in a sort of frenetic bellicosity.

From the Department of Medical History and Bibliography. University of California Medical School, San Francisco.

UNIVERSITY OF MICHIGAN LIBRARIES

The fortunate demise of a rich uncle in Carickfergus, Ireland, put the gangling adolescent in possession of several hundred pounds. With these he bought himself a horse and some good clothes and set off to improve his education and seek his fortune. After a short stay in Charlotte he descended, with a flourish, upon Salisbury, where he cut a handsome swath. He was developing what his detractors, in these and later years, called his other manners—the polished ones. In pursuing the polish he left his money far behind and, after a year, departed from Salisbury financially a ruin.

This short study of money and manners convinced Andrew that success would crown only greater effort and real concentration. He abandoned his wild oats in midfield and, after two years of determined study, passed his examinations and became prosecutor in the court of Judge John McNairy, in Nashville. He was only twenty-one which would seem callow for a prosecutor, had it not been that the Judge was only twenty-six. Andrew's courtroom manner was still a moderately adult application of his childhood aggressiveness, but, since it was usually backed by evidence, it began to help instead of hinder.

Andrew boarded with the family of John Donelson where he met Rachel Donelson Robards, estranged from her disagreeable husband and living in her father's house. The love of Andrew and Rachel was a crucial factor for it, like the inner damage inflicted by the attack of the British officer, colored every action of his life thereafter. In this woman's defense he received wounds which determined the course of his health, and, because of her, he nearly failed to win the presidency.

Robards, drunk but determined, used threats and ruses to force the return of his wife. None of the moments of best romantic tradition were slighted in the course of the affair. In 1790, worn out by the struggle, Rachel did return to her begging husband but found life so unendurable that she sent for someone to come and take her away again. Her family sent Jackson. Like the knight in shining armor he swept her away to her sister. It was an innocent voyage of desperation but it might as well have been the blackest of elopements. Rachel's reputation tottered.

Robards declared that he would sue for divorce immediately and, presumably, went off to do so. Hearing no more, Jackson and Rachel waited a proper length of time and then, in 1791, were quietly married. It is odd that Jackson, with his legal training, did not bother to make sure that all obstacles had been removed and that Rachel was a free, if sullied, character. He made a grave mistake because Rachel was not free. Her disgruntled and cunning husband had never divorced her at all. He had only gone so far as to procure an "enabling act" which gave him the right to petition, but was nothing more in itself. So, to the crime of having run away with another man's wife, Andrew Jackson added the sin of living with her for three years without benefit of marriage. In 1794 Robards tired of the game and put the divorce through. By this time our red-headed friend had become so stubborn and righteous that he had to be strongly persuaded that, for the benefit of anything that remained of Rachel's reputation, it was necessary to remarry her. After much display of Jacksonian temper and some speeches about "the eyes of God" the pair went through another ceremony. Unfortunately, by this time, no act of his could repair the damage to Rachel's good name. For thirty-seven years her husband defended her valiantly but hopelessly. In honor of what he called "The Sacred Name" he used whips, fists, and pistols on calumniators but he was never able to restore her to respectability. When he was made president the poor little woman did her best to prepare for what must have loomed to her as a hideous and endless ordeal. By the grace of some kind of Providence, on the eve of her departure for Washington, a final heart attack stepped in, and Jackson entered the White House a widower.

In 1806 ill feeling of some years standing came to a climax when Charles Dickinson publicly slurred the name of Rachel Jackson. The conduct of the resulting duel has been discussed acrimoniously for the past hundred and forty-two years, not always to the credit of Jackson, the survivor. He appeared on the field in an enormous black overcoat, which he did not remove. He was so thin that the bulk of the coat effectively disguised all the landmarks by which a duellist works and Mr. Jackson's heart was not where Mr. Dickinson had every reason to believe it belonged. Consequently the well-aimed bullet went wide of the mark, tore the chest muscles, broke a rib or two and settled in the chest cavity where it remained the rest of Jackson's life. Dickinson, having shot, was thus disarmed and forced by honor to stand still while Jackson, bleeding but not dead as he should be, took careful aim and shot him in the stomach. Dickinson died in agony some hours later. Jackson, after some histrionic nonchalance about his injuries, finally allowed himself to be examined and put to bed. It was then found that the wound was more severe than he had thought. He was more than a month in getting around again.

Through the years until 1813, when he was forty-six, run these recurrent comments, growing gradually more frequent: "I have had a severe attack of fever." "... a cold with pain in the breast and a cough." "Severe attack of dysentery," "serious intermittent fever," and, by the turn of the century, "rheumatism," especially in the right arm. He was never well, but, in his own opinion, he was never very ill. These were his years of growth, politically, militarily, and in his private life. A twentieth century man, faced with the symptoms which were beginning to appear in Andrew Jackson, would withdraw from the world and retire with misgivings to a little white cot in the sun, but Jackson lived with different opinions about health and in a glorious ignorance.

Several of his biographers, including Parton, claim that the effects of the Dickinson duel were largely responsible for the death of the old gentleman thirty-nine years later. Inasmuch as the bullet lay within his chest cavity during all these years and since the picture of his final dissolution is not one of terminal tuberculosis at all but of a combination of other things, they were right in a sense, though wrong in their major premise which was to the effect that the bullet agitated into flame the latent tuberculosis in the Jackson chest. It is doubtful, on the contrary, if Jackson ever had tuberculosis at all. True, he had occasionally complained of cough and a pain in his chest, but always after serious exposure as when he appeared at a midnight fire, on a cold wet night, without his coat or shirt. A homely diagnosis of bronchitis sounds appropriate here. The recurrent fever is accounted for by his malaria and his dysentery by the ubiquitous ameba or bacillus. The emaciation and poor color would hardly be unexpected in a body struggling against all these afflictions.

Parton claims that a fall, in 1825, tore open the wound of the Dickinson duel and re-established the process of degeneration. This statement presupposes that, in the interval, there had been an improvement. This was not true. There was only a slow but definite decline. It is true that, in 1825, Jackson did fall heavily, and that the immediate consequence was profuse pulmonary hemorrhage, but Parton and the others, in their preoccupation with the Dickinson duel, neglect to weigh other factors which became evident during the intervening years. By 1825 the sting of a bee was enough to upset the invalid.

When the bullet entered his thoracic cage and lodged there it carried with it bits of cloth, dust particles and other foreign matter. Just where the bullet went is a moot question for there was no x-ray machine. Perhaps it lay beside his heart, perhaps it impinged on his left lung. Whatever it did it immediately set up an inflammatory process and promoted an abscess nearby. Meanwhile the torn musculature of the shoulder predisposed the bruised underlying tissue to infection. There is every inducement and no deterrent to the formation of a pulmonary abscess.

In the early years of the nineteenth century, with its incomplete knowledge of respiratory disease, nearly anything which produced cough, sputum, bleeding and wasting was tuberculosis. The great strides of the nineteenth century were barely beginning and the complicated reaction of the body tissue to disease superimposed upon disease was far beyond the most informed of contemporary physicians. Jackson developed all the classic signs of tuberculosis, ergo he was tuberculous. This was excellent reasoning but it did not go far enough. In all probability the man was becoming the victim of a series of unlucky illnesses, any of which was formidable and which, all together, unhealed and unintelligently treated, lead inevitably to that dogged murderous follower of long standing suppuration—amyloid disease.

In 1813, through the unfortunate championship of the wrong man in another duel, Jackson became involved in what developed into a tavern brawl. His one-time good friends, Thomas and Jesse Benton, and assorted other people, met with Jackson and his friends and indulged in a battle which involved fists, clubs, and pistols. Jackson was shot twice by Jesse Benton, once in the already damaged left shoulder and again just below it in the left arm. There was no sauntering around this time. The weak shoulder was shattered and the second bullet did not emerge from the arm. It lay against the bone in the heavy muscle and it had, like its predecessor in the chest, introduced its contribution of cloth and dust particles. The hemorrhage was so massive that two mattresses belonging to the Nashville Inn were rendered useless for any future guest before it could be brought under control. Surrounded by all the doctors in Nashville, all but one of whom urged amputation, Jackson whispered "I'll keep the arm." He allowed poulticing with slippery elm, and, transplanted to the Hermitage, he stayed in bed for three weeks simply because he was too weak to get up. This was not the end of that wound. The arm was in a sling for six months. Never, until the bullet was removed nineteen years later did the inflammation subside. During all this time an active osteomyelitis was in progress.

While he lay coughing and sweating and aching the affairs of the nation went on. The Creek In-

UNIVERSITY OF MICHIGAN LIBRARIES

dians rose in revolt. When the report was brought to Nashville it had the anticipated effect upon the prostrate warrior. With undeniable heroism and appalling fortitude he hauled himself on his horse and went off to subdue the rebels. He could have been little better than a bedridden ruin. His shoulder was unhealed, his arm was useless and his temperature must have been prostrating since he was also in the middle of a severe attack of dysentery. Dr. Frederick May, who accompanied him, was asked, on his return, how the general had survived the trip. Dr. May's interesting but somewhat cryptic reply was that they had had to stop frequently and wash the general all over with sugar of lead to keep down the inflammation.

Sugar of lead, believed, at the time, to have some peculiar antiphlogistic action beyond its simple astringent powers, was Jackson's greatest support. He used it not only internally for his supposed tuberculosis and his chronically queasy stomach, but externally for anything that bothered him. He even used it as an eye wash when his sight began to fail. Since his specific for his dysentery was calomel, which he took in massive doses it raises the question whether, after years of constant use, some of his various discomforts might not have been increased by a touch of lead or mercury poisoning. The only other drug that he would countenance was common salt for emergency use in pulmonary hemorrhage which he backed up with the free and effective use of the lancet.

Within a few days of his wan arrival was fought the battle of Telledaga, one of the critical battles of the Creek War. Jackson was so ill that he could neither lie comfortably, nor sit. During the paroxysms of his dysentery he propped himself, in some strange manner, over two poles, from which he hung hour after hour. This brings up an interesting point since a shoulder as badly wounded as his recently had been, would not have been in much of a condition to use as a support. By what portion of his anatomy was Jackson, for several days, supported? To his misery was added the lack of food since a complete breakdown of the service of supply had thrown the army on the scrawny resources of an empty terrain. Jackson, racked with dysentery, subsisted on raw acorns and some of the entrails of an unfortunate hog.

Incredible man. Through the whole of this campaign and that which followed and ended with the Battle of New Orleans, his suffering and his endurance were beyond belief. In Mobile, the wounded arm sloughed a piece of necrosed bone which he lovingly sent to Rachel. There was hardly a moment when he was not racked with fever, nauseated and in harsh pain. Yet, if necessity demanded, he would descend from the horse on which he seemed barely able to sit and march, or fight, beside his men, until the emergency was over. It was these years which earned him the name "Old Hickory."

He arrived in New Orleans late in 1814, hailed as the country's hero. He had come to defend the city against the British attack which was momentarily expected. The citizens were beside themselves with enthusiasm for him and prepared a welcoming breakfast in the succulent manner of the best creole cooks. When he arrived he was, as usual, just recovering from a serious bout of fever and was gaunt, grey, unshaven, and disheveled. He was also very cranky and his stomach was so squeamish that, confronted with all the culinary wonders of New Orleans he ate a tablespoonful of hominy and a little milk. Disappointed to tears, the hostess of the occasion spoke with aperity about the "ugly old Kaintuck flat-boatman" who was shuffling around the beautiful floor in his muddy boots. What a catastrophe was the general!

New Orleans was shocked to its suave core, but it was game. Its leaders, realizing that battles were not won with company manners, gave him the co-operation needed during the days before the battle. Mr. Livingstone, a local aide de camp, determined to obey the social amenities in the face of outrage, summoned influential New Orleans to a dinner in his honor. New Orleans came with misgivings, but it came. Uneasily it sat, awaiting the arrival of its celebrated incubus. The door opened. Surrounded by his aides in marched a slender, bronzed, superbly erect gentleman whose well-brushed hair framed a quizzical but smiling—and shaven—face. His uniform was pressed and brushed. His high boots gleamed. His sword gleamed as a sword should do. His voice was soft and his conversation impeccable. New Orleans fell at his feet in relieved embarrassment. Now, oh what a joy was the General.

Following the battle of New Orleans the hero was more adored than ever. During the years immediately following his position in the country became such that, though he lost the election of 1824, it was plain that he was the man to watch in 1828. His career continued in the presence of constant and progressive ill-health which he made no attempt to hide. He was continually up and down though prostration was allowed to interfere with his activities as little as possible. In 1821 his chronic chest condition exacerbated into "inflammation of the lungs" and in 1822 he was laid out for four months with "violent cough and costiveness." The "costiveness" suddenly reversed

itself and became an excruciating attack of his old dysentery so that, for a time, he had as many as twenty passages in twelve hours. During this illness he complained, for the first time, of very copious sputum. He called it "great quantities of flime." The tortured bronchi had now responded to the perpetual inflammation by the establishment of a characteristic bronchiectasis which assured the patient, though he did not know it, that until the end of his days he would be harassed by "flime" which would be more and more troublesome as the time went on. So innocent was he, of the true meaning of all this sputum that he seemed to think that in coughing it up he was disposing of something valuable of himself. He said that he was sure he would be better if "I can moderately check this loss." In 1825, following the fall beloved of his biographers, he had one of his more memorable hemorrhages and tore apart the weakly healed shoulder wounded in both duels. There were already many hemorrhages in his history but he had become so hardened to them that, unless one made him especially uncomfortable, he did not always mention it.

His teeth were decaying with great rapidity, perhaps assisted by the calomel as well as by his general health. During the years 1826 to 1828 most of them disappeared and he was fitted with some false ones which he disliked and would not wear. During these years he was cursed with toothache and jaw ache and increasing headache which, by 1828, was beginning to affect his vision. The loss of the teeth cleared up the tooth and jaw aches but did nothing for the headache which became, like all the other conditions, a part of him.

In this state he won the election of 1828. What an astonishing physical specimen he was to sit in the presidential chair. Sixty-two years old, racked with pain, fainting from weakness, his constituents brought him to Washington at an unpublicized hour to spare him the overenthusiasm of the crowd. Elections being what they were, he could not be entirely secluded and in his rooms at Gadsby's he could be seen and handshaken by almost anyone. Otherwise he was hidden away and handled like fine china so that he might be well enough to take office on inauguration day. On that day, as always, he rose to the occasion. Spurning a carriage, he walked, bareheaded, to the White House.

The record of his years as President needs no recapitulation. The two terms stand highlighted by such things as his stands on Nullification, the United States Bank, the National Debt and the Spoils System. Right or wrong they were the stands of a man of power and strength. His blistering feuds with Clay, Calhoun, and Webster, to name only the most obvious, took more than the average man has to give over a period of years. His occupancy of the White House was accurately known as the Reign of Andrew Jackson and it was accomplished by a tottering scarecrow in deadly agony.

Soon after his inauguration serious changes became evident in his condition. They were not really sudden for it was the old story of the water wearing away the stone, but they were, especially to the bewildered clinical innocents of that day, dramatic and frightening. The basic septic condition was yielding to even greater sequelae.

Through the spring and summer of 1829 the President's whole system seemed out of sorts. His feet and legs began to swell so that by December they were genuinely dropsical. He complained bitterly of the pain in his chest and his shortness of breath was noticeable to anyone who was in the room with him. His headaches grew excruciating and left him for only a few hours at a time. His vision was very troublesome. He tried a seabathing holiday and came back to Washington to be felled by fever caused by "the miasma arising from a sewer being dug." His stomach was unmanageable. He had fever. In short, he had a true nephritis with those nephritic headaches that only a kidney sufferer can understand. There must have been an early cardiac decompensation with a nice rise in blood pressure. His eye grounds, had they been seen by a modern practitioner would have caused considerable correspondence between his doctors. Meanwhile, of course, the pulmonary focus of infection, the malaria, the dysentery, the osteomyelitis, and the bronchiectasis were going on, and on, and on.

The party, pleased with his administration, wanted him to run again, but their misgivings were very plainly put in a note written to Martin Van Buren, by William L. Marcy, when the question of the vice-presidency, was pressing. Said Mr. Marcy, "Of all the candidates for vice-president spoken of there is not one who possesses more than barely sufficient qualities for vice-president. General Jackson is advanced in life and to be frank with you, is in feeble health. I must say, however I wish otherwise, that I think the chances are against his lasting five years longer. With the best of those now spoken of for vice-president at our head as chief magistrate we should be in a miserable situation. . . ."

Such was his own faith in his indestructability that the President managed, when the Party quieted its fears enough to enlist him, to carry out

UNIVERSITY OF MICHIGAN LIBRARIES

a campaign which included parades on horseback, grueling field trips, speeches, banquets, and all the other performances required of presidential candidates. It was hampered by hemorrhages, bowel flare-ups, bleedings, cuppings, and collapses, but he won the second term of 1832.

In January of that year somebody, at last, persuaded him to allow the removal of the pistol ball from his left arm. His final grudging acquiescence was probably due to the fact that the pain in his chest and side was constant and increasing and he was having serious trouble with his shortness of breath. It is a question why he thought that the excision of the ball from his arm should help, though it was still, as always, inflamed and draining. Nobody mentioned the ever present bullet in his chest. The thin, yellow old man stood in his bedroom in the White House, grasped the back of a chair, and a doctor cut out the ball. Then, Mr. Jackson rolled down his shirtsleeve and went out to dinner.

The arm healed, for the first time in twenty years, but the loss of the bullet brought no relief to the pain in his chest and side. Jackson called in Dr. Philip Syng Physick, the greatest of them all. Dr. Physick said that cupping would relieve it. Cupping did nothing. Dr. Physick declared that the other bullet, lying so close to the President's heart, was of no consequence. Dr. Physick was strangely apathetic about the general condition of the patient. He said not a word about the dysentery, the swollen legs, the hemorrhages or the assorted other troubles of the invalid. Probably there were so many symptoms that Dr. Physick felt lost in a thick forest of very small trees. Perhaps he felt another sort of helplessness since his patient could not be induced to obey orders. Except for his three specifics, an occasional flier into somebody's patent pain killer and his lancet, Jackson could never be forced to do anything for his health except to lie down when driven by pain or exhaustion.

When his second term of office came to an end and Martin Van Buren was inaugurated, the events of the day must have had an uncanny resemblance to those of the Day of Days of Warren Harding. The wraithlike Jackson, like the shattered Wilson, staggered from his bed to conduct his ruddy, full-bodied successor into office before being helped out of the White House into feeble retirement with a doctor on each arm. Jackson left Washington so ill that he was accompanied as far as Wheeling by Dr. John Lawson, the Surgeon General, and from Wheeling to Nashville by other competent army surgeons who never left his side until they saw him safely into his own bed at home. It was a journey of three weeks and it seemed quite possible that he would never make it.

Everything was wrong with him. Amyloidosis is not often seen these days of quick relief of inflammation for it is a condition brought about by chronic suppuration. When established it is implacable. It is the only condition which can account for the grisly last years of the patient and miserable sufferer.

After 1834 he seldom had as much as an hour free from pain. His chest, his side, his short breath, all contrived to keep him in agony. His stomach refused almost anything except rice and milk. His right eye, by 1837, failed in earnest. He described it as a "white something approaching the sight" and treated it with weak sugar of lead. In 1838 during a crisis of fever and delirium his head and ear swelled to alarming proportions and his head broke out "all over soars" which he thought a very good thing. His shortness of breath precluded any exercise except a few supervised steps around his estate, always ending at Rachel's grave. His days were a procession of all his chronic symptoms with a myriad of painful, if passing, additional ones.

In this shocking state he had the temerity to travel to New Orleans for a celebration in his honor. En route he hemorrhaged so badly that it was many hours before the bleeding could be controlled and when he arrived he was too ill to make more than a token appearance. Yet, when it was over he managed to get to Jackson, Mississippi where he allowed himself to be the reason for more festivities for two days and nights. Then, after ten days in Vicksburg, he, somehow, got back to the Hermitage and when he arrived remarked, in a pleased way, that his health was about the same as it had been before he left.

This was his last long trip. Once or twice thereafter he tried to ride a little but he had to give it up. 1841 and 1842 dragged by with endless days of pain. He gave up trying to eat with the family and subsided into his invalid chair. He thought his left lung completely destroyed. In 1843 he was acutely ill, if more ill he could be, with bilious colic and cholera morbus as though he were not contending with enough without an attack of gastroenteritis. By this time the amyloidosis had reached nearly every organ in his body.

He gave up his little walk to Rachel's grave. By 1844 he could not walk at all. He lost the power of voluntary motion and was lifted from his sitting position in bed to the same position in his chair. His mind was as clear as ever and with what strength he had he insisted on making constant attacks on his still endless correspondence.

His letters show no diminution of the masterful intellect which seemed to be the only part of him decently alive. By 1845 this beautiful mind rested in a body which was nothing more than a decaying mass. In May, 1845 he wrote to Andrew Jackson Donelson that "... I am swollen from the toes to the crown of my head and in bandages to my hips. Have had a violent bowell complaint which averaged six to eight passages in twenty-four hours with a constant nausea at my stomach." He told Francis Blair, at the same time, that he was a perfect mass of jelly from his toes to the upper part of his abdomen. The distended flesh of his dropsical legs had probably broken down, thus necessitating the bandaging. The dysentery and the nausea, a thousand times exaggerated by the progress of the amyloidosis, gave him no respite. Then, as the ultimate of cruelty, the poor old man had hemorrhoids.

At this very late date a painter was sent from France to make a portrait of the old hero. It was very late. The edema had become so pronounced that the artist could use only the brow and the bushy white head and was forced to take the rest of the face from a painting made several years earlier. It was an agony for the patient to sit for his portrait at all.

The end was at hand. On June 2, 1845 his belly had become so distended that Dr. Esselman of Nashville came hurriedly to tap him. It was a useless effort for the relief was negligible and the patient was exhausted. He sat miserably, propped up in bed, unable to lie down. He could not eat.

He could not die. Under opiates for his pain he drifted in and out of consciousness until Sunday, June 8th. All that day he was moribund until suddenly, at sunset, he opened his eyes. His adopted son asked whether he could recognize him, to which he answered tartly that of course he could and that he would recognize the others around his bed if someone would kindly fetch his glasses. When they were brought, he wiped them neatly on the sheet and perched them on his nose. There was a sentence or two, a sigh and a feeble chuckle. He was gone, as though, all at once, he had decided he had fought too long.

REFERENCES

1. PARTON, JAMES. Life of Andrew Jackson. 3 vols. New York: Mason Bros., 1860.
2. BASSETT, JOHN SPENCER (ed). Correspondence of Andrew Jackson. 6 v. Washington, D.C.: Carnegie Institute of Washington, 1926.
3. JAMES, MARQUIS. Andrew Jackson: The Border Captain. New York: Bobbs-Merrill Co., 1933.
4. Idem. Andrew Jackson: A Portrait of a President. New York: Bobbs-Merrill Co., 1937.
5. BUELL, A. C. History of Andrew Jackson. 2 vols. 1904.
6. BRADY, CYRUS TOWNSEND. The True Andrew Jackson. Philadelphia: J. B. Lippincott Co., 1906.
7. BOWERS, CLAUDE G. The Party Battles of the Jackson Period. Boston: Houghton Mifflin, 1922.
8. Encyclopedia Brittanica, 14th ed.
9. Boston M. S. J., 1847, 5: 36.
10. Dispensatory of the United States of America, 24th ed. 1947.
11. SQUIRE, PETER. Companion to the last edition of the British Pharmacopoeia, 1869.
12. GOLDBERG, BENJAMIN (ed). Clinical Tuberculosis. 2 vols. Philadelphia: Davis, 1942.
13. FLINT, AUSTIN. Principles and Practice of Medicine. Philadelphia: Lea Brothers, 1886.
14. OSLER, WILLIAM, and MCCRAE, THOMAS. Modern Medicine. Philadelphia: Lea & Febiger, 1914.
15. CHRISTIAN, HENRY A. Principles and Practice of Medicine. New York: D. Appleton-Century Co., 1944.
16. CECIL, RUSSELL A. A Textbook of Medicine. Philadelphia: W. B. Saunders Co., 1937.
17. FAGGE, C. H., and PYE-SMITH, P. H. Textbook of Medicine. 2 vols. Philadelphia: The Blakiston, Co., 1902.

UNIVERSITY OF MICHIGAN LIBRARIES

REVIEWS OF NEW BOOKS

THE second edition of Dr. Mettler's *Neuroanatomy*[1] is an improvement over the first edition, which was published in 1942. Not only have many of the minor errors been corrected but the author has added a number of new and noteworthy illustrations. One of the principal features of merit is the incorporation in a textbook of neuroanatomy of illustrations and descriptive material for the gross anatomy of the cranium and especially the blood vessels therein. Functional and clinical aspects of the subject have been woven into the fabric of the book and make it especially useful for the advanced reader. On the other hand, the inclusion of much detailed and some controversial material detracts from its usefulness as a textbook for beginning students of medicine.

WILLIAM F. WINDLE.

THE monograph, *Strabismus; a Clinical Handbook*,[2] directed primarily to the ophthalmologist, deals with the practical clinical methods of examination, diagnosis, and treatment of strabismus. It is not a large book since it contains only 204 pages with 76 plates and drawings.

The book is separated into six chapters divided according to anatomy, physiology of binocular vision, normal muscle balance, concomitant strabismus, paralytic strabismus, and strabismus surgery.

Considerable attention has been given to the significant contributions of Sherrington in the physiology of binocular perception and Chavasse in the development and mechanism of normal and abnormal binocular reflexes, in the hope that more effort will be diverted toward clinical and laboratory study with less emphasis on abstract speculation.

The book contains an outlined method of procedure for working up the patient with concise instructions as to the technique for prism measurement in the six diagnostic, or cardinal, positions of gaze. This is accompanied by a simplified explanation of measurements and their significance. In the chapter on concomitant strabismus the treatment is directed toward correcting the cause and the pathological conditions established by the strabismus. Very little space is devoted to orthoptic training and it is gratifying to note that the author realizes that it is of limited value. The section on surgery gives specific procedures and exact techniques for operating upon the various muscles but the illustrations and the discussion on inferior oblique surgery seems inadequate.

The book is well written and it will be of value to ophthalmologists and all practitioners interested in strabismus.

IRVING PUNTENNEY.

[1]NEUROANATOMY. By Fred A. Mettler, A.M., M.D., Ph.D. 2nd ed. St. Louis: The C. V. Mosby Co., 1948.

[2]STRABISMUS; A CLINICAL HANDBOOK. By George J. Epstein, B.A., M.D. Philadelphia and Toronto: The Blakiston Co., 1948.

IN her book *Breast Feeding*[3] the author has given many helpful suggestions and ideas gleaned from years of clinical study, avoiding as much as possible detailed technical data. Most of this material, however, is substantiated by scientific investigations.

Breast milk is not offered as the food of all infants. It is suggested that the mother's attitude and problems be thoroughly considered and investigated. The doctors who are willing to take the time and effort to discuss these factors with the mother and particularly the prospective mother, will be in a better position to judge which women should nurse. Furthermore, such conferences give the physician an excellent opportunity to present the real reasons for nursing.

The properties of cow's milk and human milk are reviewed and the superior qualities of breast milk as an infant food are listed. It is stated that colostrum apparently does not have any specific value; therefore, the expression of this secretion daily for 3 months prior to the expected birth of the baby may be advisable. This procedure, learned from the experience of dairymen, has reduced the incidence of mastitis and enhanced the early flow of milk.

Some different points on how to establish breast feeding in the first week of the infant's life are set forth along with sound reasons for the use of both breasts at each feeding. The stipulation to use only a spoon to give a complementary feeding will no doubt meet with some disapproval. The author's suggestion that large infrequent feedings in infancy will dilate the stomach and avoid anorexia in childhood, may also be questioned.

The technique for manual expression of breast milk is given in detail, offering many helpful suggestions about a lost art.

This small volume, devoted entirely to breast feeding, reviews and brings to focus a neglected phase of modern medicine.

L. MARTIN HARDY.

IN the seventh edition of *Recent Advances in Obstetrics and Gynecology*,[4] Bourne and Williams do not presume to review all of the newest and most recent developments in obstetrics and gynecology. Rather, as the senior author stated in the preface to the first edition, they attempt to present that new work which has been tested sufficiently to establish it as of real practical and prominent value and to record movements of thought and trends of opinion.

[3]BREAST FEEDING. By F. Charlotte Naish. London, New York, and Toronto: Geoffrey Cumberlege Oxford University Press, 1948.

[4]RECENT ADVANCES IN OBSTETRICS AND GYNECOLOGY. By Aleck W. Bourne, M.A., M.B., B. Ch. (Camb.), F.R.C.S. (Eng.), F.R.C.O.G., and Leslie H. Williams, M.D., M.S. (Lond.), F.R.C.S. (Eng.), F.R.C.O.G. 7th ed. Philadelphia and Toronto: The Blakiston Co., 1948.

The text is divided into sixteen chapters each of which is in essence, a monograph on a particular subject. In that portion devoted to obstetrics, the chapters on weight changes and water retention in pregnancy, lactation, erythroblastosis and radiology in obstetrics, by E. Rohan Williams, are particularly worthy of commendation. The discussion of lactation is an excellent summary of material not ordinarily available to the clinician.

Part II, devoted to gynecology, contains chapters on cancer of the cervix, stress incontinence, sympathectomy, penicillin in gynecology, radiological investigation and diagnosis in gynecology, and x-ray therapy in gynecology. Many American readers will be surprised to find that the cytological diagnosis of genital cancer is not mentioned. The Aldrige modification of the Goebel-Stoeckel operation for urinary incontinence is shown in detail. The chapter on sympathectomy deals primarily with the value of sympathetic nerve block in femoral thrombophlebitis.

The text as a whole is an interesting commentary on a number of pertinent obstetrical and gynecological subjects.

JOHN HUFFMAN.

THE name "Devine" is associated with the names of present-day leaders in the field of colonic and rectal surgery. The written word from such a source, therefore, is not to be taken lightly. It is no doubt a source of embarrassment to the publishers that the name is spelled "Divine" on the binding. As is stated in the preface, an attempt has been made to reflect the knowledge and wisdom that has been accumulated by the authors on the subject matter, and the book accomplishes that purpose.

The book, *The Surgery of the Colon and Rectum*,[1] is of convenient size, has good print and is well illustrated with diagrammatic drawings and photographs. In most instances, the color illustrations seem to be substandard and not essential. Color, however, usually has its advantages.

The subject matter deals with the usual and unusual benign and malignant lesions and has been arranged most carefully, with a resultant ready reference book for the intern, resident, or full-fledged surgeon. The amount and variety of detail contained in the book are surprising and would presuppose dull reading but that is not the case; it is very easy reading and is without verbosity. Sentences are short, concise and to the point. Case reports are numerous and well selected to drive home specific lessons.

It would appear that the omission of figures and statistics has been deliberate since there are practically none in the 362 pages. It has been said that statistics can prove anything, sometimes even the truth. Despite the lack of statistics, the book is of practical value. From it, one will get the authors' reasoning and answers to many questions that one has or should have regarding the problems of colonic and rectal diseases.

All surgeons will not agree, although this reviewer does, with the statement, "The so-called aseptic anastomosis of the colon has not materially reduced the mortality rate." Neither is there unanimity of opinion regarding the advisability of side-to-side anastomosis, as compared with end-to-side or end-to-end anastomosis.

It is evident that the authors prefer multiple stage procedures in the majority of instances of resectable lesions of the right or left portions of the colon, whereas the general trend in this country has been more and more toward one stage operations. The authors' preference is justified on the basis of their statement, "We feel that primary anastomosis of the distal colon, especially segmental resection of the rectosigmoid, should be reserved for the highly organized clinic."

It is a bit disturbing to one whose training and experience have led him to avoid vaseline intraperitoneally to read of the free use of it on the exploring glove.

The experienced surgeon knows that there are many efficient surgical methods of arriving at the same objective. The purpose of the Devine book is not to cover the entire subject but to present the summation of their experience in the field it covers. The book is excellent from this viewpoint and is well worth becoming fingermarked from use by the student, medical or surgical, regardless of age.

CHARLES W. MAYO.

WHEN Professor Minder went to lecture at Zurich at the end of 1944 the war prevented his return to Budapest so he utilized this involuntary vacation for a review of his knowledge in the remaining fields of medicine. He discovered that among the many good textbooks there were only a few which could serve as guides for the less experienced. He decided, therefore, to present urology by explaining first the most important urological problems and in the form of lectures in *Lehrbuch der Urologie*.[2] In this way he was enabled to describe in great detail topics of practical interest such as tuberculosis of the kidneys, disease of urinary calculi, and hypertrophy of the prostate, and to discuss problems which apparently lie outside the field of urology but which are important from the viewpoint both of the practitioner and specialist.

Simple methods of examinations and the use of special urological instruments cannot be taught without practical demonstrations. A detailed description of them is of little advantage for the general practitioner. Whatever the author has found as essential in this regard (such as introduction of catheters, the practice of massage of the prostate, or the essentials of lithotripsy, etc.) has been explained by diagrams.

The author did not have his library or clinical resources and very little of the comprehensive statistical data of the urological clinic in Budapest and the urological surgical department of the city of

[1] THE SURGERY OF THE COLON AND RECTUM. By Sir Hugh Devine, M.D., and John Devine, M.D. Baltimore: The Williams and Wilkins Co., 1948.

[2] LEHRBUCH DER UROLOGIE. By Prof. Dr. Med. J. Minder. Bern: Hans Huber, 1946.

UNIVERSITY OF MICHIGAN LIBRARIES

Budapest with him in Zurich, so the greatest part of the lectures had to be composed without notes or the utilization of previous publications. He apologizes for omitting the names of authors which had escaped his memory and for not giving references to articles published on the subjects he has written about. All of his conceptions are based on his personal experience gained in large urological departments over a period of 25 years.

The lectures are 25 in number, covering 317 pages with 35 diagrams, about 23 pictures of pyelograms, and 20 photographs, mostly of specimens. The first lecture is a chronological history of the development of a modern urological clinic—Guyon's clinic for diseases of the urinary tract. The invention of the cystoscope by Nitze in 1888, the development of the ureteral catheter and the retrograde pyelogram, better method of sterilizing instruments, improved anesthesia, and the development of kidney function tests all contributed to the reduction of the mortality rates of prostatectomy from 30 or 35 per cent to from 3 to 8 per cent and of nephrectomy from 15 to 25 per cent to from 2 to 4 per cent.

The problem of prostatectomy—suprapubic versus perineal—urinary antiseptics, the development of intravenous pyelography, the resectoscope and transurethral prostatic resection, and, finally, chemotherapy, hormone therapy, and penicillin therapy are discussed in the first part of the book.

The remaining 24 lectures cover the problems of urological symptoms, renal function and renal diagnosis from the urological standpoint, renal tumors and nephroptosis. Tuberculosis of the kidney, ureter, bladder, and genitalia are well covered. The only important therapeutic measure not included is the use of streptomycin.

The lectures on urinary calculi are excellent. Those on diseases and pathological conditions of the bladder are well written as are the lectures on prostatic hypertrophy. The author discusses the theories of hypertrophy, the methods of removal of the gland, treatment of complications, and he includes mention of hormonal therapy.

Infections of the bladder, prostate, seminal vesicles and epididymis of gonorrheal and nongonorrheal origin and the modern therapy of each are well discussed.

Less important or rare diseases have only been touched upon in a brief appendix. These include epispadias, hypospadias, enuresis, prostatism, prostatic abscess, orchitis, epididymitis acute or chronic, varicocele, and urethral strictures.

The alphabetical index is well and effectively arranged.

KNOWLTON E. BARBER.

GRAY'S *Anatomy of the Human Body*[1], now in its 90th year of publication, has recently (July, 1948) been published in its 25th American edition. While no fundamental changes have been made in the plan of this justly famous book, a few changes in text, figures, and editorial policy are noted, which may or may not meet with the approval of all anatomists.

The most significant change noted relates to editorial policy. The editorial board of seven professional anatomists has been discontinued in favor of one man editorship. It is not likely that this change in editorial policy will be of immediate importance since the encyclopedic anatomies of this type are changed but little from one edition to the next. In the long run, however, a doubt may be entertained as to one man's competency in the several branches of anatomy to maintain all sections of such a comprehensive work in a state of up-to-date and authoritative revision.

Other changes noted pertain to text, figures, and table of contents.

Only the text of the section on muscles and fascias shows evidence of extensive revision. Muscles are treated individually in regard to action and nerve supply. This is not new, but is a reversion to the arrangement followed in most of the standard texts a few editions back. This straightforward treatment of muscle action is much to be preferred over the descriptions by groups as in the 24th edition of Gray and recent editions of other standard texts. Medical students have no difficulty in grasping the concept of synergistic and antagonistic action of muscles, but they do find it unnecessarily time consuming to dig out individual muscle action from the group descriptions in the previous edition and in other texts. The concept of group action is not sacrificed, but is considered appropriately following the study of individual muscle actions. A tedious section on the mechanics of muscle action has been omitted.

Descriptions of regional fascial layers have been amplified and improved. This is an important addition which might well have been carried further.

The table of contents has been condensed from 18 to 4 pages, a great improvement from the standpoint of convenience and utility.

No change is made in the old half functional and half anatomical classification of joints. This reviewer favors the classification of the three major types on a morphological basis: fibrous, cartilage, and synovial. This classification puts the emphasis on development and structure, where it logically belongs.

A slight concession to practical anatomy is noted in a reference to J. F. Huber's system of bronchopulmonary segments. The section on surface and topographical anatomy impresses the writer as a completely useless appendage. It is too sketchy to be of practical use and a great deal of its material is taken from other sections of the book. What little new material there is in this section might well be incorporated in other appropriate sections of the book.

The illustrations in the 25th edition are brighter and a few new ones have been introduced, but there

[1]ANATOMY OF THE HUMAN BODY. By Henry Gray, F.R.S. 25th ed. Edited by Charles Mayo Goss, M.D. Philadelphia: Lea & Febiger, 1948.

is still a serious lack of cross sections and other types of sectional figures.

One concept of anatomy exemplified in early editions was that of its usefulness to surgery. Brief comments on regional surgical applications are interspersed throughout the original text. All such practical references have been excluded from recent American editions as a threat to the purity of the science. Many teachers of the basic medical sciences appear to entertain a great fear of contamination by any reference to useful application. Gray was apparently in agreement with the reviewer in his belief that scientific method and thought must be carried through to the so called clinical years and into practice if the highest possible standards of medical education and medical practice are to be achieved. Investigations begun for a practical purpose may lead to profound philosophical deductions, and the reverse may also be true.

The fact that Gray's *Anatomy* has enjoyed great prestige for almost a century, without significant change in plan or arrangement of subject matter, is a great tribute to the author, who incidentally, was only thirty-one when the first edition was published. It is no tribute, however, to modern generations of anatomists that no modern text has appeared to compete with Gray or the other bulky texts. In Gray's time the term anatomy covered the field. Now medical students are required to supply themselves with texts of histology, embryology, neuroanatomy, and gross anatomy. Yet the great and bulky old anatomies retain sections on these subdivisions which are now inadequate to meet the needs of medical students, teachers, or physicians. Students pay for material they do not use, and get an unwieldly book which, in modern regional dissection and study of gross anatomy, is extremely inconvenient and wasteful of the student's time.

What medical students need is a textbook of gross anatomy, designed to meet present day teaching methods, mostly regional in arrangement, with more functional implications, better illustrations, and a more straightforward, readable text.

SYDNEY EVANS JOHNSON.

SINCE 1925, when *Treatment by Manipulation in General and Consulting Practice*[1] first appeared it has remained a classic in the field of manipulative surgery. The fifth edition contains much new material, with numerous illustrations which enhance its value.

The author's approach to the subject is well balanced and refreshing. There is no attempt made to set forth manipulation as a panacea for all joint disease. Advantages, disadvantages, indications and contraindications are clearly described, and details pertaining to each joint are discussed. The conditions which may be benefited by manipulative treatment are confined to four main groups: articular or periarticular adhesions; subluxations and dislocations of joints, tendons or intra-articular discs; adhesions in connection with muscles, tendons, or fascia; and certain functional or hysterical conditions of joints and of the spine.

The first five chapters deal with the historical background, the pathology, the prevention and diagnosis of adhesions, and the general principles of manipulative treatment. The remainder of the book is devoted to a detailed discussion of the joints of the upper and lower extremities, the spine, and the sacroiliac joints. This discussion includes a description of the anatomy, prevention of deformity, indications for manipulation, and technique. Case histories illustrating the use of manipulative surgery in each joint discussed are included. The concluding chapters are rather sketchy, but endeavor to point out the possible dangers of manipulation, and the need for adequate after care.

The book is the result of many years of experience and mature evaluation by the author in the field of manipulative surgery. It is a work that should be in the library of all who are concerned with joint diseases.

WILLIAM A. LARMON.

THE comprehensive and inclusive report, *Nursing for the Future*[2], prepared by Dr. Brown is both a challenge and a constructive awakening to the nursing profession as well as allied professions. Science in all of its many phases, industry, economics, business, and sociology have kept pace with one another in rapid advancement in order to remain an integral part of modern civilization.

It is the responsibility of the nursing profession to attain and maintain standards of nursing which are comparable and on a level with the educational trends of today. This endeavor cannot be accomplished without co-operation from other professional forces involved nor can it be accomplished through traditional standards and reminiscences. It must be a direct straightforward move with discretional disregard for time-worn measures and custom.

We must maintain adequate nursing care which is both quantitatively sufficient and qualitatively efficient. With this point in mind it becomes necessary to consider nursing from a comprehensive point of view. There must be no differentiation in our basic attitude which will divide professional graduate nurses from licensed practical nurses. Nursing functions must be considered in a like manner.

The role of the graduate registered nurse today and in the future is one of supreme importance and responsibility. It is a task which, in order to be successfully accomplished, requires the aid of co-operative assistants including practical nurses, attendants, and other subsidiary workers. Therefore, personal and personnel relationships within all fields of nursing must be in complete rapport in order to allow for co-operative and efficient functioning.

[1] TREATMENT BY MANIPULATION IN GENERAL AND CONSULTING PRACTICE. By A. G. Timbrell Fisher. 5th ed. New York and London: Paul B. Hoeber, Inc., 1948.

[2] NURSING FOR THE FUTURE. A Report Prepared for the National Nursing Council. By Esther Lucile Brown, Ph.D. New York: Russell Sage Foundation, 1948.

UNIVERSITY OF MICHIGAN LIBRARIES

The burden of this increased responsibility is accordingly greater for the registered professional nurse and she must be theoretically and practically trained to execute her role. She must be trained and educated to the extent that she will possess the knowledge and ability to supervise constructively and instruct other nurses and subsidiary workers to formulate and develop new techniques in nursing care, and contribute to world wide health movements on an equal plane with allied professions.

Professional nursing education today is on a university level, therefore, nursing services to maintain progress must be reorganized. The conditions found in many schools of nursing today are incredible. They are not schools in any sense but rather means for student exploitation partially disguised by the organization of the hospitals concerned.

Dr. Brown's report was published under the auspices of the Russell Sage Foundation. The National Nursing Council promoted this study concerned with the reorientation of nursing education.

Concisely and precisely this report contains the following recommendations for nursing education at the present time and in the future that:

1. The profession take steps to study thoroughly and examine every school of nursing and publish and circulate freely a list of accredited schools of nursing.
2. The necessity for increasing salaries and prestige be thoroughly considered and results expedited.
3. Nonprofessional nurse programs of training be established and maintained on a national basis with definite prerequisites for licensure.
4. The nursing profession establish and maintain definite levels of professional achievement in order that promotions and advancement will be governed by preparation, experience, and achievement.
5. The nursing profession allow for education of the public to the problem at hand, and thereby obtain co-operation, support, and participation.

The health and hygiene needs of society today prompted this study and Dr. Brown has extensively and intensively presented these needs as well as recommendations for meeting them in a modern progressive manner. These recommendations are only the beginning for the reorientation of the profession and it is the responsibility of each and every member of nursing to participate whole-heartedly in this great movement. KATHERINE E. BALTZ.

BOOKS RECEIVED

Books received are acknowledged in this department, and such acknowledgment must be regarded as a sufficient return for the courtesy of the sender. Selections will be made for review in the interests of our readers and as space permits.

TRANSACTIONS OF THE SOUTHERN SURGICAL ASSOCIATION. Vol. 69. Fifty-ninth Annual Meeting, Hollywood Beach, Florida, Dec. 9, 10, 11, 1947. Edited by Alfred Blalock. Philadelphia: J. B. Lippincott Co., 1948.

ANESTHESIA: PRINCIPLES AND PRACTICE. By Alice M. Hunt. New York: G. P. Putnam's Sons, 1949.

SHOCK AND ALLIED FORMS OF FAILURE OF THE CIRCULATION. By H. A. Davis, M.D., C.M., F.A.C.S. New York: Grune & Stratton, 1949.

TWENTY-THIRD MEETING OF THE NORTHERN SURGICAL ASSOCIATION HELD IN STOCKHOLM, JUNE 26TH TO 28TH, 1947. Edited by Prof. E. Dahl-Iversen, M.D., Secretary-General. Copenhagen: Ejnar Munksgaard, 1948.

CLINICAL ENDOCRINOLOGY FOR PRACTITIONERS AND STUDENTS. By Laurence Martin, M.D.(Camb.), F.R.C.P. (Lond.), and Martin Hynes, M.D.(Camb.), M.R.C.P. (Lond.). Philadelphia and Toronto: The Blakiston Co., 1949.

CANCER OF THE ESOPHAGUS AND GASTRIC CARDIA. Edited by George T. Pack, B.S., M.D. St. Louis: The C. V. Mosby Co., 1949.

THE BRITISH ENCYCLOPAEDIA OF MEDICAL PRACTICE INCLUDING MEDICINE, SURGERY, OBSTETRICS, GYNAECOLOGY AND OTHER SPECIAL SUBJECTS. Medical Progress, 1948. Edited by Rt. Hon. Lord Horder, G.C.V.O., M.D., B.Sc., F.R.C.P. London: Butterworth & Co., Ltd., 1948.

VETERANS ADMINISTRATION TECHNICAL BULLETINS. Series 10, 1946 and 1947. Washington: Veterans Administration, 1948.

THE NORMAL AND PATHOLOGICAL PHYSIOLOGY OF PREGNANCY. Proceedings of the Conference of the Committee on Human Reproduction of the National Research Council on Behalf of the National Committee on Maternal Health, New York City, January 1948. Reprinted from Obstetrical and Gynecological Survey. Vol. 3, No. 5, October 1948. Baltimore: The Williams & Wilkins Co., 1948.

COLLATERAL CIRCULATION (ANATOMICAL ASPECTS). By Daniel P. Quiring, Ph.D. Illustrated by Margaret Holman. Philadelphia: Lea & Febiger, 1949.

SURGICAL TECHNIQUE AND PRINCIPLES OF OPERATIVE SURGERY. By A. V. Partipilo, M.D., F.A.C.S. 4th rev. ed. Philadelphia: Lea & Febiger, 1949.

CLINICAL ASPECTS AND TREATMENT OF SURGICAL INFECTIONS. By Frank Lamont Meleney, M.D., F.A.C.S. Philadelphia and London: W. B. Saunders Co., 1949.

INMOVILIZACION; VENDAJES TRACCION CONTINUA ENYESADOS. By Dr. Jose Pedro Reggi. Buenos Aires: Lopez & Etchegoyen, 1948.

NEUROVEGETATIVO. By Estanislao Lluesma-Uranga. Buenos Aires: Lopez & Etchegoyen, 1948.

HALLUX VALGUS. By Carlos Khoury. Buenos Aires: Lopez & Etchegoyen, 1947.

MEDICINA PSICOSOMATICA; APLICACIONES CLINICAS DE LA PSICOPATOLOGIA A LA MEDICINA GENERAL. By Edward Weiss and O. Spurgeon English. Buenos Aires: Lopez & Etchegoyen, 1949.

THE 1948 YEAR BOOK OF GENERAL SURGERY. Edited by Evarts A. Graham, A.B., M.D. Chicago: The Year Book Publishers, 1949.

MANUAL OF CLINICAL LABORATORY METHODS. By Opal E. Hepler, Ph.D., M.D. 4th ed. Springfield, Ill.: Charles C Thomas, 1948.